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Treatment of the Cardiac Arrhythmias

TRAVIS WINSOR AND NICHOLAS J. KHOURY*

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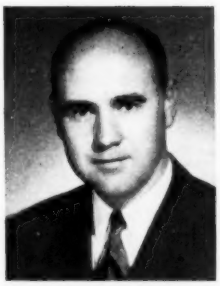
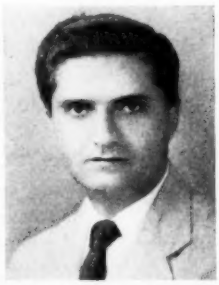
FIFTY years have passed since the description of the string galvanometer by Willem Einthoven in 1903. This instrument has facilitated the study of the cardiac arrhythmias, and has made it possible to analyze in detail the effects of many drugs used for the treatment of these irregularities. In the early part of the century, Sir James Mackenzie, by employing the polygraph, also made notable contributions relative to the identification of the cardiac arrhythmias and their treatment with certain drugs. During the past half-century, many new drugs have been employed, and their actions have been carefully studied by means of modern electrocardiographic and other technics.

It is the purpose of this report to summarize the experience gained in treating the cardiac irregularities over the past 50 years by evaluating the work of other authors in the light of personal experience. The paper is intended to be comprehensive in that most of the commonly employed and some of the new agents are discussed. The details of administration of these agents are outlined to provide the reader with practical information of clinical value. In many instances, the treatment outlined is didactic, and it is realized that other treatment regimens may serve equally well.



TRAVIS WINSOR



NICHOLAS J. KHOURY

There are at least four basic principles which govern the treatment of patients with cardiac irregularities. These are: (1) treatment of the basic disease, (2) maintenance of blood pressure, (3) prevention or treatment

*From the Heart Research Foundation, Hospital of the Good Samaritan and the Department of Medicine, University of Southern California, Los Angeles, California.

Some of the newer drugs were studied with financial aid from the Los Angeles Heart Association.

of cardiac decompensation, and (4) control of the arrhythmia.

Treatment of the Basic Disease

Cardiac irregularities may be caused by various disease processes. When these are corrected, the cardiac rhythm will be restored to normal. Some diseases which cause cardiac irregularities are hyperthyroidism; hypothyroidism; rheumatic fever; coronary artery disease; anemia; electrolyte disturbances; nephritis; vitamin deficiencies (e.g., beriberi), and toxemias or infections such as diphtheria, infectious mononucleosis and subacute bacterial endocarditis. Certain drugs which are used to treat cardiac irregularities, for example, digitalis and quinidine, also are capable of producing these irregularities, and discontinuance of the administration of these drugs often is sufficient to restore a normal sinus rhythm.

Maintenance of Blood Pressure

The blood pressure should be determined frequently during therapy of cardiac arrhythmias as certain drugs, such as quinidine and PRONESTYL® (procaine amide), have a hypotensive effect. If the blood pressure falls as the result of peripheral vasodilatation, intravenous administration of 0.6 cc. of a 0.1 per cent solution of NEO-SYNEPHRINE® hydrochloride (phenylephrine hydrochloride) will elevate the pressure acutely, but this effect lasts only about three minutes. One-half cubic centimeter of a 1 per cent solution of this drug may be administered intramuscularly, and the frequency of administration may be determined by the blood pressure level. When the drug is administered in this manner, the duration of its action is about 20 minutes. The intravenous administration of 4 cc. 1 per cent Neo-synephrine hydrochloride in 1000 cc. of a 5 per cent aqueous solution of dextrose by the drip method will produce a sustained effect. The rate of administration also should be determined by the blood pressure level.

Neo-synephrine is a useful drug because it slows the cardiac rate without producing serious cardiac irregularities, coronary constriction or increased cardiac work. It has a direct constricting effect on the peripheral arterioles, and this is the mechanism by which the blood pressure is elevated. The pulse rate is slowed reflexively as a result of the increased pressure in the carotid sinus and aortic arch.

Four milligrams of LEVOPHED® bitartrate (l-norepinephrine bitartrate) in 1000 cc. of a 5 per cent aqueous solution of dextrose may be administered intravenously by the drip method. The hypertensive effects of Levophed are similar to those of Neo-synephrine. This drug is more potent than Neo-synephrine and its effects are more difficult to control. It may be used, however, if Neo-synephrine is ineffective.

VASOXYL® hydrochloride (methoxamine hydrochloride) should not be given to patients with coronary artery disease but is a suitable hypertensive agent if the coronary circulation is normal. The dose is 5 mg. for intravenous administration and 15 mg. for intramuscular administration. Twenty-five milligrams of ephedrine sulfate may be administered intramuscularly every four hours, but it is a less suitable agent since it produces cardiac acceleration, increases cardiac work, and may initiate ectopic beats and ventricular tachycardia or fibrillation.

Prevention of Cardiac Decompensation

Successful treatment of congestive heart failure often improves cardiac irregularities. The drug of choice for the treatment of congestive heart failure is digitalis, especially when combined with a diuretic regimen and a low sodium diet.

Control of Cardiac Arrhythmias

Most cardiac irregularities are caused by either overstimulation or depression of the myocardium, the sympathetic nervous system, the parasympathetic nervous system or some combination of these factors. The drugs useful for treating these abnormalities are those which have a normalizing effect on the structure or system involved. The anatomy of the efferent nerve pathways of the parasympathetic and sympathetic nervous systems is shown in figure 1. In this figure, it can be seen that the sympathetic system has fibers which innervate the ventricles whereas the

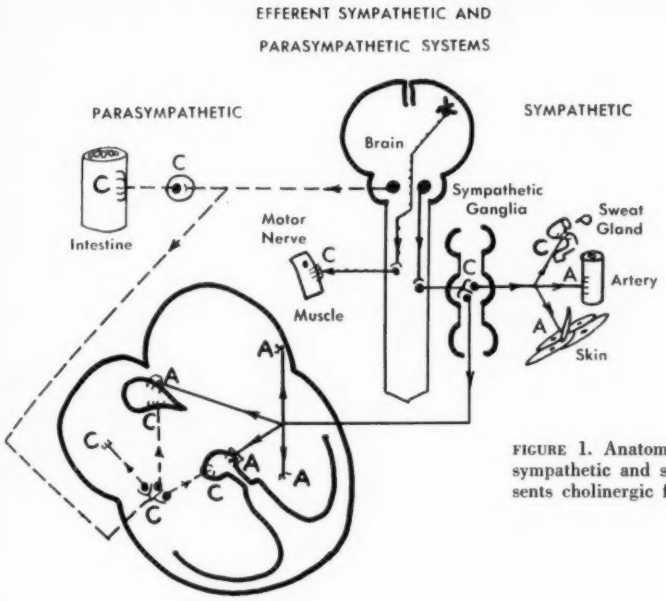


FIGURE 1. Anatomy of efferent pathways of the parasympathetic and sympathetic nervous systems. C represents cholinergic fibers; A represents adrenergic fibers.

parasympathetic system does not innervate this structure. Both systems innervate the auricles, the sinus and the A-V nodes.

The cardiac rhythm is controlled for the most part by the relative concentrations of two chemical substances, acetylcholine from the parasympathetic system and epinephrine or epinephrinelike substances which are liberated from the nerve endings of the sympathetic system. The concentration of these substances depends on the relative activities of the two systems which are stimulated by afferent impulses from the soma and viscera traveling within the sympathetic and parasympathetic nerves to the cardiac center in the brain (figure 2). Efferent sympathetic impulses travel from the brain through the cord and sympathetic ganglia to the auricles, ventricles, sinus and A-V nodes. A relatively high concentration of epinephrine at the auricles produces auricular ectopic beats; at the sinus node, it produces sinus tachycardia; at the A-V node, accelerated A-V conduction results, and, at the ventricle, ectopic beats are produced. High concentrations of acetylcholine present at the auricles depress auricular contraction, delay impulse formation at the sinus

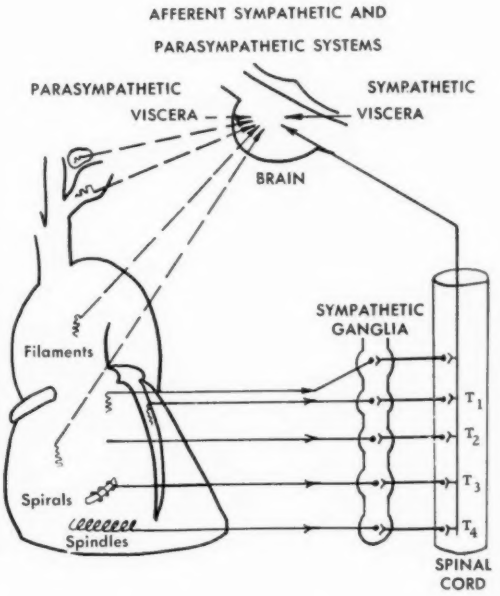


FIGURE 2. Afferent impulses from the soma and viscera travel within the sympathetic and parasympathetic nervous systems to the brain.

node with resultant sinus bradycardia, and slow A-V conduction, thus producing a first or second degree A-V block.

Sinus Arrhythmia

This is a rhythmic alteration in heart rate associated with respiration. Normally, it occurs as the result of reflex cyclic changes in vagus tone. It is produced by stimulation of the vagus, inhibition of the sympathetic nerves or both, and is accentuated by deep breathing. The afferent limb of the reflex arc is from the lungs to the vasomotor center, and the efferent limb is from the vasomotor center to the sinus node. Sinus arrhythmia is abolished by breath-holding, exercise, drugs, general anesthesia or fever. It is found normally in children and elderly persons, and pathologically it occurs with brain damage which produces an irritable parasympathetic nervous system. Treatment usually is not necessary; however, if desired, 50 mg. of BANTHINE® bromide (methantheline bromide) may be administered orally every four hours.

Sinus Bradycardia

This is defined as a cardiac rate below 60 beats per minute which originates from a pacemaker in the sinus node (figure 3). It is due to (1) an increased vagal tone which produces an increase in the amount of acetylcholine at the sinus node and thus slows the rate, (2) a decreased sympathetic tone which allows a relative overbalance of the parasympathetic system, or (3) an inherent slow myocardial rhythmicity. It may be acute or chronic. Sinus bradycardia may be associated with acute gastric distention, vomiting, biliary or renal colic, myocardial infarction, hypersensitivity of the carotid sinus, hypothyroidism, malnutrition, pregnancy, jaundice, meningitis, typhoid fever and diphtheria. It also may be caused by digitalis, quinidine, and most parasympathomimetic drugs. It may occur during sleep, in athletes and in some normal persons who have not had athletic training.

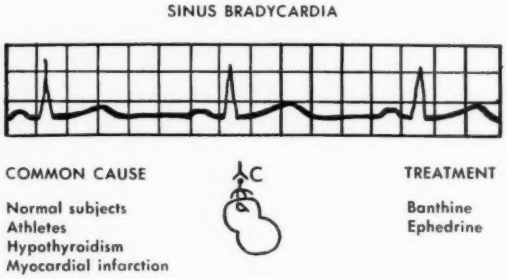


FIGURE 3. Cholinergic vagus fibers innervate the sinus node, and their stimulation causes sinus bradycardia.

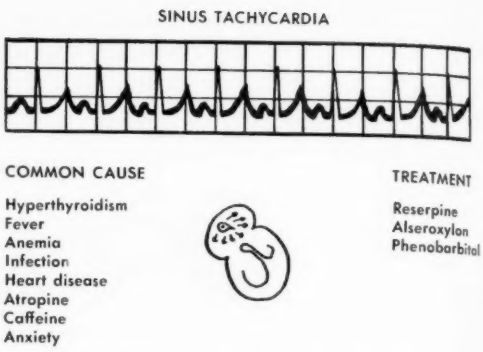


FIGURE 4. A pacemaker in the sinus node which discharges at a rapid rate is a common cause of sinus tachycardia.

Treatment of this arrhythmia is not necessary unless the heart rate is slow enough to interfere with the cardiac output. Treatment consists of correcting the underlying disease process, and administering parasympathetic blocking agents such as Banthine and sympathomimetic drugs such as ephedrine. Fifty milligrams of Banthine bromide is administered orally every four hours, or 25 mg. is administered intramuscularly every six hours. Three-eighths of a grain of ephedrine sulfate is administered orally three times a day, or 10 mg. is administered intramuscularly every six hours.

Sinus Tachycardia

This is defined as a cardiac rate greater than 100 beats per minute for adults, the heart being driven by a pacemaker in the sinus node (figure 4). It is caused by overstimulation of the sinus node by the sympathetic nervous sys-

tem, inhibition of the parasympathetic system, inherent rapid myocardial rhythmicity, or a combination of these factors. Factors which stimulate the sympathetic nervous system are worry, fear, painful stimuli, or various sympathomimetic agents, such as BENZEDRINE® (racemic amphetamine sulfate) or DEXEDRINE® (dextro-amphetamine). Inhibition of the parasympathetic system is produced by many commonly employed antispasmodics, such as atropine. Factors which affect the rhythmicity of the heart directly are fever, thyrotoxicosis, acidosis, neoplasms, caffeine, nicotine and cardiac disease. Other causes of sinus tachycardia are anemia, beriberi, neurocirculatory asthenia, respiratory distress and shock.

Treatment consists of removing the cause, if possible, and decreasing anxiety by giving 0.25 mg. of reserpine or 2 to 4 mg. of RAUWILOID® (the alseroxylon fraction of Rauwolfia serpentina) at night or 0.5 gr. of phenobarbital three times a day.

Sinus Arrest

This is a temporary depression of the sinus node which results in transient standstill of the auricles and ventricles for one or several beats (figure 5). If sinus arrest is prolonged and no other cardiac structure takes over as pacemaker, cardiac standstill results. Sinus arrest is caused usually by increased vagal tone which depresses the sinus node by means

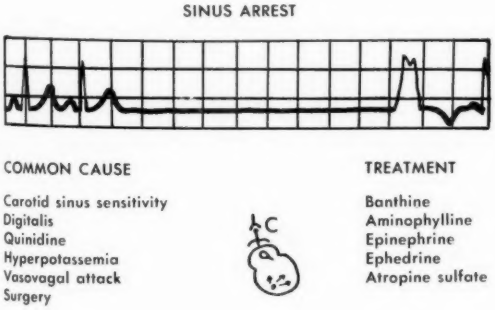


FIGURE 5. Cholinergic inhibition of the sinus node is a common cause of sinus arrest. Ventricular escape beats may occur as a result of a pacemaker in the ventricles and stimulate ventricular contractions.

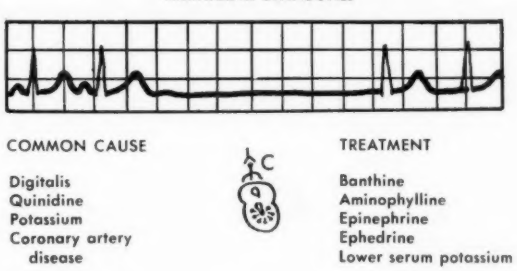


FIGURE 6. Cholinergic inhibition of the sinus node inhibits auricular contraction. In the example, a pacemaker in the bundle of His drives the ventricles.

of high concentrations of acetylcholine in the region of this structure. It may also be caused by a hypersensitive carotid sinus, digitalis, quinidine, surgery (especially in and around the thorax) and psychogenic shock. Figure 5 shows a period of sinus arrest with a ventricular escape beat which caused ventricular contraction after which normal sinus rhythm occurred.

In cases of recurrent sinus arrest, the administration of any offending drug should be discontinued, and 50 mg. of Banthine bromide should be administered orally three times a day. Three-eighths of a grain of ephedrine sulfate may be administered orally three times a day to produce cardiac acceleration, and 3 gr. of aminophylline may be given orally at similar intervals to stimulate the myocardium directly.

For the treatment of acute attacks, 1/300 gr. of atropine sulfate may be administered intravenously or by intracardiac injection, and this may be followed by the intracardiac injection of 1 cc. of a solution composed of 1 part of a 1:1000 solution of epinephrine and 9 parts of physiologic saline solution. One cubic centimeter of this solution contains 0.1 mg. of epinephrine. Larger doses of epinephrine may be indicated in some cases, but such doses are dangerous because they may cause ventricular fibrillation.

Surgical denervation of the sensitive carotid sinus or intracranial division of the glossopharyngeal (ninth cranial) nerve on the sen-

sitive side has been carried out in cases of chronic or recurrent hypersensitivity of the carotid sinus. If complete cardiac standstill occurs, sternal frappage often will result in the restoration of normal cardiac rhythm. In using this procedure, the physician places his left hand over the sternum and strikes the hand sharply with his right fist. The first evidence that cardiac rhythm is being restored may be the development of a cardiac irregularity. Sternal frappage may be used before using electric stimulators or before opening the thorax for cardiac massage.

Auricular Standstill

This is a cessation of auricular contraction resulting from disease or depression of the sinus node (figure 6). In this condition, the auricles fail to beat but the ventricles continue to contract. Depression of the sinus node may be due to increased vagal tone, which can be abolished by the intravenous administration of 1/300 gr. of atropine or by the intramuscular administration of 1/150 gr. of this drug. Digitalis, quinidine and Pronestyl also will depress the sinus node. Injury of the sinus node may be due to coronary artery disease or other cardiac disease.

Auricular standstill may be associated with hyperpotassemia. It usually occurs when the value for the serum potassium is 10 mEq. per liter or higher. In cases of hyperpotassemia, the concentration of serum potassium should be lowered by a low potassium diet, by the intravenous administration of 20 cc. of a 10 per cent solution of calcium gluconate three times a day, by the intravenous administration of 1000 cc. of a 10 per cent aqueous solution of dextrose twice a day, by the administration of 8 units of crystalline insulin twice a day before meals, by the intramuscular administration of 100 mg. of cortisone acetate three times a day for four or five days, or by the administration of 30 mg. of potassium-free exchange resin* daily by mouth or in an enema.

When auricular standstill is due to coronary insufficiency, coronary dilators, such as PERITRATE® (pentaerythritol tetranitrate), are administered with drugs such as aminophylline and ephedrine sulfate which have a stimulating effect on the myocardium. Peritrate is administered four times a day in doses of 10 mg., aminophylline is administered orally, three times a day, in doses of 3 gr., and ephedrine sulfate is administered orally, three times a day, in doses of 3/8 gr.

*This drug is manufactured by the Smith, Kline & French Laboratories of Philadelphia. At present, it is available only for clinical investigation.

Premature Contractions

Premature beats are cardiac contractions which occur early in time. Ectopic beats are contractions arising from an abnormal site in the heart, and extrasystoles are added beats (figure 7). These beats may arise from the auricles, the A-V node or the ventricles, and may be caused by any process which interferes with the nourishment or metabolism of the myocardium. Ectopic beats, especially ventricular beats, usually are not indicative of cardiac disease when their onset is early in life and when they disappear with exercise. They usually are indicative of cardiac disease when they appear late in life and are brought on by exercise. Treatment of ectopic beats is not necessary if the beats are benign or infrequent and do not disturb the patient unduly.

Auricular premature contractions may be caused by organic disease or chemical irritation of the auricles, e.g., hyperthyroidism, infections or anesthetics, especially ether; or they may be produced by overstimulation of the sympathetic nervous system by excitement or stress. Oral administration of 3 gr. of quinidine sulfate four times a day usually is effective in controlling the auricular premature contractions regardless of cause. As an alternative, 500 mg. of Pronestyl hydrochloride may be administered orally, three times a day, but this is considerably less effective.

Nodal premature beats may be *primary* as a result of overstimulation of the A-V node by means of the sympathetic nervous system, chemical agents or organic disease, or they may be *secondary* to depression of the sinus node. Administration of 3 gr. of quinidine sulfate, four times a day, usually is effective against nodal premature beats of the primary type. Parasympathetic blocking agents, such

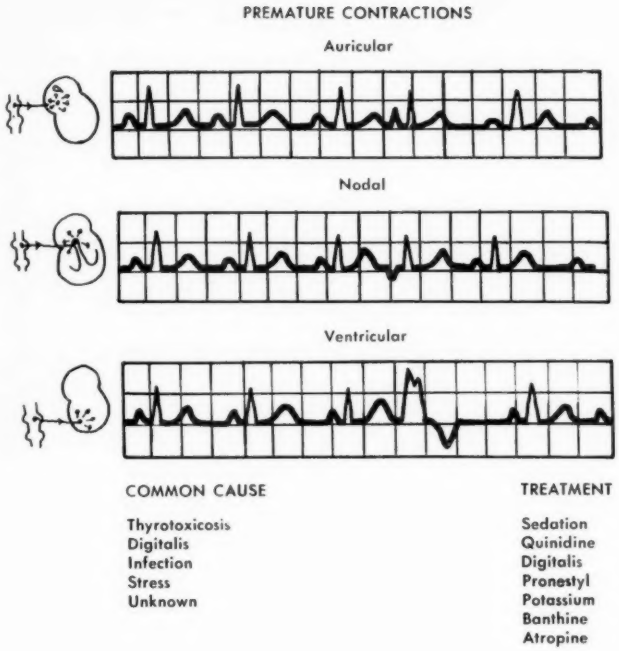


FIGURE 7. Premature contractions may result from sympathetic stimulation of the auricles, A-V node or ventricles, or from an irritable focus in these structures.

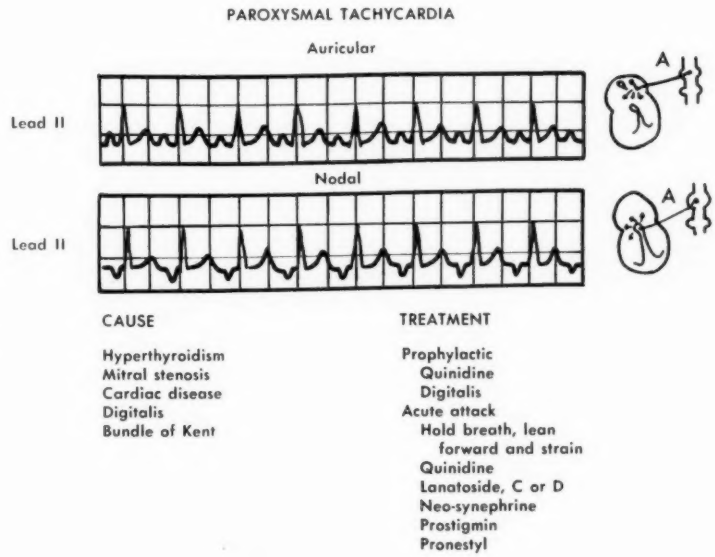


FIGURE 8. Adrenergic sympathetic fibers innervate the auricular musculature and A-V node. Sympathetic stimulation of irritable foci in these structures causes paroxysmal tachycardia.

as Banthine bromide, usually are effective against premature beats of the secondary type. This drug is administered orally, four times a day, in doses of 50 mg.

Ventricular premature beats may be caused by organic disease, or chemical irritation of the ventricles, such as results from excessive amounts of epinephrine, caffeine, nicotine or alcohol, or by overstimulation of the sympathetic nervous system. Unifocal ventricular premature contractions, when occasional, may not be of clinical significance. Multifocal ventricular premature contractions usually are indicative of the administration of excessive amounts of digitalis or of the presence of severe organic disease.

The oral administration of 3 gr. of quinidine sulfate four times a day is more effective than the oral administration of 500 mg. of Pronestyl hydrochloride three times a day. Digitalis frequently is effective when ectopic beats are associated with heart failure; however, this drug also may cause ventricular premature beats, especially if it is given in large doses. When these beats are due to an excess of digitalis, the oral administration of 2 gm. of potassium chloride three times a day for two or three days or the oral administration of 50 mg. of Banthine bromide four times a day usually is effective. The administration of the digitalis should be discontinued.

Paroxysmal Tachycardia

Paroxysmal tachycardia in an adult is diagnosed when the cardiac rate is greater than 100 beats per minute and when the heart is driven by a pacemaker in the auricle or A-V node (figure 8). It may be caused by hyperthyroidism, mitral stenosis, coronary artery disease, bundle of Kent syndrome (Wolff-Parkinson-White syndrome), smoking, alcohol, gastrointestinal upsets, infection, and tumors and space-occupying lesions of the mediastinum. It also may occur in persons who apparently are normal and who do not appear to have any cardiac disease.

Auricular tachycardia may result from an organic lesion in an auricle, chemical stimulation of the auricles, stimulation of the sympathetic nervous system or depression of the parasympathetic nervous system.

Nodal tachycardia may be primary or secondary. Primary nodal tachycardia is due to organic or chemical stimulation of the A-V node or to relative stimulation of the sympathetic nervous system. Secondary nodal tachycardia is due to depression of the sinus node.

An acute attack of paroxysmal tachycardia should not be considered a cardiac emergency since most attacks are of short duration and terminate spontaneously. If the attacks are due to drugs or to systemic disease, the administration of the offending drug should be discontinued and the underlying disease should be treated. Treatment that is hazardous should not be employed because of the benign nature of most of the attacks.

The treatment of paroxysmal auricular tachycardia is as follows: The patient should sit on the edge of the bed, hold his breath, and lean forward and strain. He then should lie in bed and elevate his legs in the upside-down bicycle position to increase the pressure in the carotid sinus. The recommended treatment includes the oral administration of 6 gr. of quinidine sulfate and ¾ gr. of NEMBUTAL® every four hours until four doses have been given. The patient should rest in bed until the attack ceases.

The intravenous administration of 6 cc. of liquid CEDILANID® (lanatoside C), which contains 1.2 mg. of lanatoside C and is two-thirds of the digitalizing dose, or the intramuscular administration of a similar dose of CEDILANID-D® (desacetyl lanatoside C) usually is effective, especially if pressure is applied to the carotid sinus 20 to 30 minutes after the drug is given. Intramuscular administration of 1 cc. of a 1:2000 solution of PROSTIGMIN® (neostigmine) sometimes is effective.

Another drug that has proved effective is Neo-synephrine hydrochloride, administered intravenously by the drip method in a dose of 2 cc. of a 1 per cent solution in 500 cc. of physiologic saline solution. The rate of administration should be sufficient to elevate the blood pressure about 15 per cent, and the solution should be given under electrocardiographic control.

Intravenous administration of 100 mg. of

Pronestyl hydrochloride every two minutes also is effective. The total dose should not exceed 750 mg. The blood pressure should be taken every three minutes while the drug is being administered, and Neo-synephrine hydrochloride should be used to elevate the blood pressure if necessary. The intravenous administration of 0.6 cc. of a 0.1 per cent solution of this drug or the intramuscular administration of 0.5 cc. of a 1 per cent solution usually is sufficient. Large doses of Pronestyl hydrochloride should not be administered without electrocardiographic control.

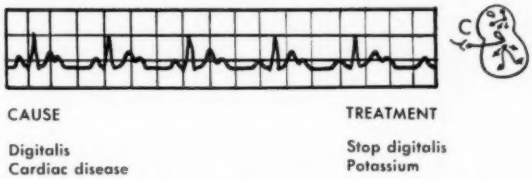
Pressure on the carotid sinus may be used when the patients are young, but it should not be used in treatment of elderly persons because the pressure might result in cerebral anemia and hemiplegia. Also the use of pressure on the eyeballs has caused detachment of the retina.

Since MECHOLYL® (metacholine) has a drastic action, it usually is not indicated. It may be used, however, if atropine is available for intravenous administration. Vasoxyl hydrochloride has been administered intravenously in cases in which there was no evidence of coronary artery disease. It should not be used if this disease is present. Apomorphine and ipecac are undesirable because of their side effects. They are unnecessary because better forms of treatment are available.

Prophylactic treatment is indicated if the attacks occur more frequently than every three months and are of long duration, if there is an underlying cardiac disease which makes the attacks detrimental to the patient, or if the patient suffers from undue anxiety as a result of the attacks. Oral administration of 12 gr. of quinidine daily in divided doses usually is adequate. If this is not effective, powdered digitalis leaf may be used. If the patient is of average size, 1.5 gm. of this drug is given in divided doses in a period of five days. Thereafter, 0.1 gm. may be given daily.

The treatment of *paroxysmal nodal tachycardia* that is secondary to depression of the S-A (sino-auricular) node consists of the administration of parasympathetic blocking agents, such as Banthine bromide, and stimulation of the S-A node by the use of aminophylline. Banthine bromide is administered intravenously in doses of 3 to 5 mg. Three grains of aminophylline may be administered orally three times a day, 3¾ gr. in 10 cc. of sterile water may be given intravenously twice a day, or 7½ gr. in the form of a rectal suppository may be given twice a day. If nodal tachycardia is due to stimulation of the A-V node, 3 gr. of quinidine may be administered orally or intramuscularly four times a day. Larger doses may be necessary.

PAROXYSMAL AURICULAR TACHYCARDIA WITH BLOCK



CAUSE	TREATMENT
Digitalis	Stop digitalis
Cardiac disease	Potassium

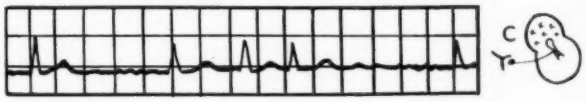
FIGURE 9. Irritable foci in the auricles and bundle of His with inhibition of the A-V node, often through vagal stimulation, result commonly from digitalis and produce paroxysmal auricular tachycardia with block.

Paroxysmal Auricular Tachycardia with Block

This is characterized by a rapid series of auricular contractions arising from a pacemaker in the auricle with irregular conduction through the A-V node to the ventricle (figure 9). It usually is caused by digitalis intoxication, but it may occur in patients with organic cardiac disease who are not receiving digitalis.

In cases in which it is due to digitalis, the administration of the drug should be stopped,

AURICULAR FIBRILLATION



CAUSE	TREATMENT
Hyperthyroidism	Prophylactic
Infarction	Quinidine
Infection	Acute attack
Mitral stenosis	Digitalis
Coronary insufficiency	Quinidine
Hypertension	
Digitalis	

FIGURE 10. Auricular fibrillation is produced by multiple irritable foci in the auricles with an irregular ventricular response.

and 2 gm. of potassium chloride or potassium citrate should be administered orally, four times a day, for two or three days. Potassium should be given carefully to patients with renal disease because it might cause hyperpotassemia which produces cardiac depression. In emergencies, slow intravenous administration of 3 or 4 gm. of potassium chloride in 500 cc. of a 5 per cent aqueous solution of dextrose, under electrocardiographic control, is effective in restoring sinus rhythm. If this fails, Pronestyl hydrochloride or quinidine sulfate may be administered intravenously.

Auricular Fibrillation

This is a state of rapid fibrillatory movements of the auricles with ventricular contractions which occur irregularly and at a slower rate (figure 10). The auricles are ineffective as a pump, and functionally they remain in diastole. Although auricular fibrillation almost always is caused by cardiac disease, it may occur in normal persons or it may be caused by myocardial infarction, acute rheumatic carditis, acute infections, mediastinal tumors, hyperthyroidism, rheumatic mitral stenosis, hypertension, constrictive pericarditis or coronary artery disease. It also may be caused by digitalis and other drugs.

The cause of the fibrillation should be treated if possible. This applies particularly to hyperthyroidism and active rheumatic heart disease. In a high percentage of cases in which the fibrillation has been present for less than six weeks, it can be converted to sinus rhythm by the administration of quinidine sulfate; in cases in which it is of longer duration, it often is refractory to treatment, and it can be converted to sinus rhythm in only about 50 per cent of these cases. In more than half of the cases in which the fibrillation is converted in this manner, it recurs within six months. The attempted conversion carries with it a mortality rate of 2 to 5 per cent owing to emboli from the auricles or the toxic effects of the quinidine sulfate.

Treatment of the fibrillation is by intensive administration of quinidine sulfate as follows: On the first day, 3 gr. every two hours for five doses; on the second day, 6 gr. every two hours for five doses; and, on the third day, 9 gr. every two hours for five doses. Larger doses of quinidine sulfate usually are not tolerated well. After the fibrillation has been converted to sinus rhythm, this rhythm should be maintained by the oral administration of 12 gr. of quinidine sulfate daily in divided doses.

It recently has been advocated that, to help prevent embolism, an anticoagulant such as heparin should be administered every 12 hours for five days before an attempt is made to convert the fibrillation to sinus rhythm. A concentrated aqueous solution of heparin (200 mg. per cubic centimeter) is used. The dose of the drug is based on the body weight, and is as follows: 200 mg. per 100 pounds, 250 mg. per 150 pounds, and 300 mg. per 200 pounds.

A $\frac{3}{4}$ in. No. 26 needle is used, and the solution is injected deeply into the subcutaneous tissue over the iliac bone to avoid intramuscular injection. A track of highly concentrated material is left by injecting the drug while the needle is withdrawn. The coagulation time is determined before the initial injection and before every second injection. The

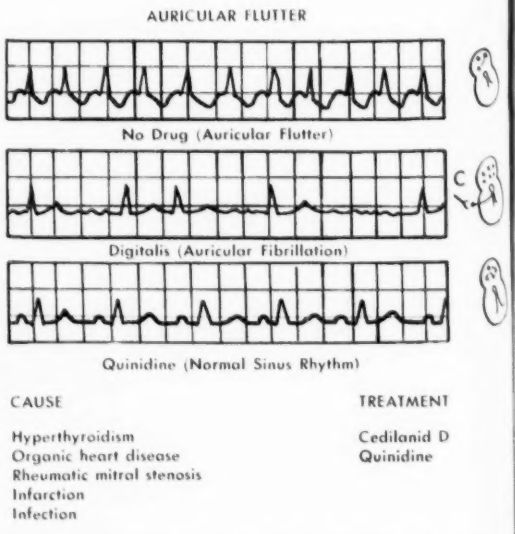


FIGURE 11. Upper tracing: auricular flutter which often is produced by an irritable focus in the auricles. Middle tracing: auricular fibrillation produced by digitalis. Lower tracing: sinus rhythm which appeared when digitalis was stopped and quinidine was administered.

dose is reduced if the coagulation time is longer than 30 minutes.

If the cardiac rate is rapid and if conversion of the fibrillation to sinus rhythm is not desirable, the cardiac rate may be slowed by the administration of digitalis. Digitalis leaf, 1.5 gm., is administered in divided doses in a period of three to five days, with a maintenance dose of 0.1 gm. daily thereafter. This type of treatment is quite satisfactory, especially if the venous pressure, circulation time and vital capacity are normal at the completion of the treatment.

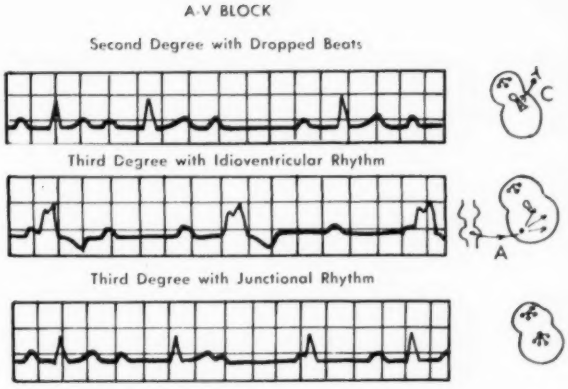
Auricular Flutter

This is a rapid series of auricular contractions usually occurring at a rate of less than 350 per minute (figure 11). The ventricular rate is equal to or less than the auricular rate. Auricular flutter is a serious cardiac irregularity because of the rapid rate at which impulses are conducted to the ventricles. Conversion of this irregularity to sinus rhythm is somewhat safer than the conversion of auricular fibrillation because emboli at the periphery are less likely to occur. Auricular flutter is more likely to be transient than auricular fibrillation; however, persistent auricular flutter does occur. Auricular flutter occurs commonly with organic cardiac disease, such as chronic rheumatic valvular disease, rheumatic myocarditis, hypertension, acute infections, hyperthyroidism and arteriosclerotic heart disease. It is produced commonly by quinidine and rarely by digitalis.

Cardiologists do not agree regarding the treatment of auricular flutter; however, it is agreed that this arrhythmia should be converted to sinus rhythm if at all possible. The treatment of an acute attack is as follows. A short-acting, rapidly dissipated, digitalizing agent is administered on an intensive schedule in an attempt to convert the auricular flutter to auricular fibrillation. Cedilanid-D is used for this purpose. A full digitalizing dose (8 cc.*) is administered immediately by the intramuscular route; 2 cc. is given two hours later, and a similar dose is given at the end of another two hours.

An electrocardiogram should be taken before the injection of the first dose, two hours after the third injection, and before each subsequent injection, in order to detect the onset of digitalis toxicity as evidenced by a prolonged P-R interval or ectopic beats. Additional doses of 2 cc. are given intramuscularly at intervals of two hours until signs of toxicity (nausea and characteristic electrocardiographic changes) appear or until the auricular flutter is converted to auricular fibrillation.

If auricular fibrillation occurs, no more Cedilanid-D is given for three days in order



CAUSE	TREATMENT
Congenital heart disease	Prophylactic
I-V septal defect	Discontinue drugs
Infection	Banthine
Rheumatic fever	Coronary dilator
Coronary artery disease	Peritrate
Drugs	Ephedrine
Quinidine, Pronestyl,	Aminophylline
Digitalis	Syncopal attack
Toxic states	Norisodrine
Diphtheria	Isuprel
Uremia	Epinephrine
Vagal stimulation	
Carotid sinus	

FIGURE 12. Upper tracing: second degree A-V block with dropped beats. This often results from vagal inhibition of the A-V node or from organic disease of this structure. Middle tracing: third degree A-V block with idioventricular rhythm. This usually results from organic disease of the A-V node with a pacemaker in the sinus node and in the ventricles. Lower tracing: third degree A-V block with junctional rhythm. This usually is due to organic disease of the A-V node with pacemakers in the sinus node and in the junctional tissue.

*Cedilanid-D is supplied in ampules for intramuscular or intravenous administration. Each cubic centimeter of the solution in the ampules contains 0.2 mg. of the drug.

to allow the drug to be excreted from the body. Often, auricular fibrillation reverts spontaneously to normal sinus rhythm. If this does not occur, quinidine sulfate should be administered on an intensive schedule as described previously. If sinus rhythm occurs, a maintenance dose of 12 gr. of quinidine sulfate is administered daily in divided doses. If this treatment is not effective, digitalis and quinidine sulfate may be administered together.

In cases of auricular flutter, the patient is digitalized to prevent congestive heart-failure and to prevent a 1:1 conduction which would result in a rapid ventricular rate. This occurs commonly after administration of quinidine sulfate has slowed the auricular contractions. Two electrocardiograms should be made daily to detect bidirectional, ventricular, ectopic beats, which may result from the simultaneous administration of quinidine and digitalis, and often precede ventricular fibrillation and death.

In the prophylactic treatment of auricular flutter, approximately 12 gr. of quinidine sulfate is administered daily in divided doses. Larger doses are necessary in some cases.

Auriculoventricular Block

There are three types of auriculoventricular block: (1) first degree block, which is characterized by a prolongation of the P-R interval without dropped ventricular beats; (2) second degree block, which is characterized by dropped beats (this may or may not be of the Wenckebach type), and (3) third degree block, in which there is an independent beating of the auricles and ventricles (figure 12).

Third degree auriculoventricular block with idioventricular rhythm is diagnosed when the electrocardiogram reveals evidence of two cardiac pacemakers, one above the A-V node (usually the sinus node) and the other below the A-V node in the ventricle. The electrocardiogram shows wide QRS complexes and a ventricular rate which is considerably slower than the auricular rate.

Third degree auriculoventricular block with nodal or junctional rhythm is diagnosed when two pacemakers are present, one above the A-V node, usually in the sinus node, and the other below the A-V node in the junctional tissue. The electrocardiogram shows QRS complexes which are not unduly wide and a ventricular rate which is only slightly slower than the auricular rate.

Auriculoventricular block may be due to functional or organic heart disease. First degree A-V block is sometimes functional and is due to increased vagal tone, whereas second and third degree blocks usually are due to organic disease of the A-V node. Various causes of A-V block are coronary artery disease; drugs such as quinidine, Pronestyl and digitalis; rheumatic heart disease involving the A-V node; congenital heart disease, especially interventricular septal defects; toxic states; uremia, and myxedema. A-V block often is associated with syncope due to ventricular standstill or ventricular fibrillation.

The treatment of first or second degree A-V block is as follows: The underlying disease process should be treated. If the block is due to digitalis or quinidine, the administration of these drugs should be stopped. If it is due to coronary artery disease, a coronary dilator such as Peritrate, 10 mg. three times a day, should be used.

A dose of 1/300 gr. of atropine sulfate should be administered intravenously, under electrocardiographic control, to determine if the block is due to excessive vagal tone. If the block is corrected by this drug, 50 mg. of Banthine bromide is given orally every four hours. If the block persists after the administration of the atropine, direct-acting myocardial stimulants, such as aminophylline, ephedrine sulfate, PAREDRINE® hydrobromide and barium chloride, are used. Aminophylline is administered orally, 3 gr. four times a day, or 7½ gr. in a rectal suppository is given every six hours. Ephedrine sulfate is administered orally, three times a day, in doses of ⅜ gr. Paredrine hydrobromide is administered orally, three times a day, in doses of 20 mg., and barium chloride is administered four times a day in doses of 10 mg. Barium chloride is not employed commonly because it is likely to cause ventricular fibrillation.

Quinidine and other myocardial depressants are contraindicated here because they may

cause a greater degree of A-V block. Digitalis should be used with great caution, but it should be used if congestive heart failure is present.

The objective of the treatment of third degree A-V block is to prevent ventricular arrest or ventricular fibrillation and to establish sinus rhythm. To accomplish this objective, the drugs used for the treatment of first and second degree block should be employed as outlined previously, but other agents are necessary. When the ventricular rate becomes very slow, for example, 20 to 25 beats per minute, the patient should take three inhalations of a powder containing 25 per cent of NORISODRINE® sulfate (isopropylarterenol sulfate), or 15 mg. of ISUPREL® hydrochloride (isopropylarterenol hydrochloride) should be administered sublingually.

The results of the treatment of acute attacks of syncope, that is, Stokes-Adams attacks, are uncertain. It should be determined electrocardiographically whether the attacks are due to ventricular fibrillation or to ventricular arrest. If they are due to ventricular fibrillation, the intravenous administration of Pronestyl hydrochloride is indicated, but this drug must be given cautiously because ventricular arrest frequently follows its administration. If this should happen to occur, a sharp blow on the chest occasionally is effective in starting ventricular contractions, and this should be tried. Intracardiac injection of 0.1 mg. of epinephrine may be used if the blow on the chest is ineffective.

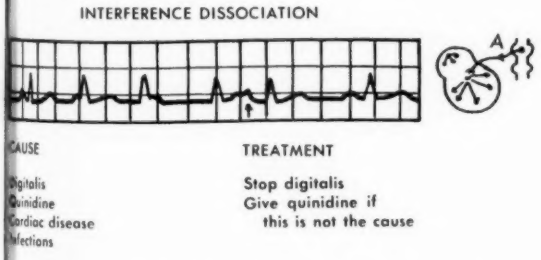


FIGURE 13. Interference dissociation is caused by two pacemakers, one in the sinus node and one in the A-V node. Incomplete interference dissociation is shown in this illustration.

When auriculoventricular block occurs in the course of an operation, other methods of treatment are necessary. In certain cases, electric defibrillation and periodic stimulation of the heart by direct or indirect application of electrodes may be practical.

Interference Dissociation

This is an independent beating of the auricles and ventricles, the ventricular rate being the same or slightly faster than the auricular rate. Auriculoventricular dissociation may be incomplete or complete (figure 13).

Incomplete auriculoventricular dissociation results from two pacemakers competing with each other for dominance. The sinus node stimulates the auricles and the A-V node stimulates the ventricles. Usually, the auricular activation wave cannot advance to the ventricles because of the refractory period of the ventricles. Occasionally, however, a sinus stimulus reaches the A-V node early enough to cause ventricular contraction with normal conduction from the auricles to the ventricles.

In complete interference dissociation, sinus impulses are not transmitted through the A-V node at any time, and the auricles and ventricles always are beating independently of each other. Auriculoventricular dissociation may be caused by drugs such as digitalis; by infections such as rheumatic fever, diphtheria and pneumonia; and by myocardial infarction.

If the dissociation is due to an underlying disease, the disease should be treated; if it is due to digitalis, the administration of this drug should be discontinued. Quinidine may be useful to decrease the cardiac irritability.

False Bundle-Branch Block

False bundle-branch block (Wolff-Parkinson-White syndrome), which also is called anomalous atrioventricular conduction, is a condition characterized by a typical electrocardiogram which exhibits short P-R intervals and wide QRS complexes. Patients with this type of tracing are prone to have attacks of rapid heart action, such as auricular, nodal or ventricular tachycardia, auricular flutter or fibrillation, or other irregularities. In certain instances, this condition is due to transmis-

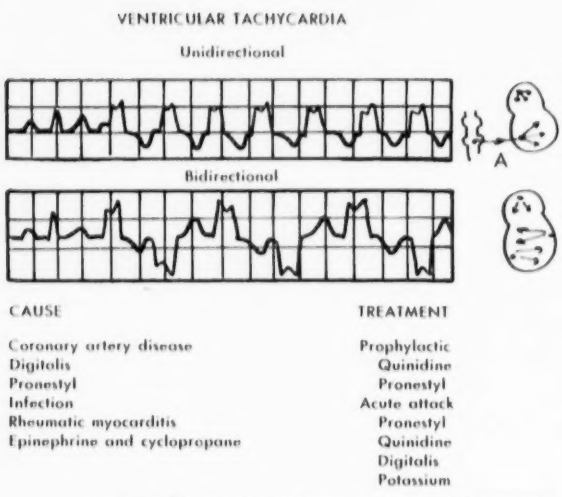


FIGURE 14. Ventricular tachycardia is caused by ectopic pacemakers in one or both ventricles.

sion of the auricular accession wave along an accessory muscle bundle, the bundle of Kent, which runs from the auricles to the ventricles. Treatment is not required unless cardiac arrhythmia develops. At this time, quinidine is the drug of choice, although other agents may be employed for the particular cardiac irregularity which develops.

Ventricular Tachycardia

This is a rapid series of ventricular contractions independent of auricular activity and arising from an irritable focus in the ventricle (figure 14). The QRS complexes may originate from a single focus (unidirectional), or from multiple foci (bidirectional). The ventricular rate varies from 100 to 300 beats per minute. This arrhythmia may be caused by digitalis; Pronestyl; epinephrine, especially when this drug is administered with cyclopropane; coronary artery disease; myocardial infarction; rheumatic fever, or a bundle of Kent.

Ventricular tachycardia is a cardiac emergency, and it should be treated immediately. The cause of the arrhythmia should be removed. If it is due to digitalis or other drugs, the administration of the offending drug should be discontinued. Pronestyl hydrochloride in doses of 100 mg. may be administered intravenously every two minutes under electrocardiographic control, the total dosage not to exceed 750 mg. The blood pressure should be taken every three minutes while this drug is being administered. If hypotension should develop, 0.6 cc. of a 0.1 per cent solution of Neo-synephrine hydrochloride should be administered intravenously.

If the Pronestyl hydrochloride is not successful in controlling the attack, 0.3 gm. of quinidine gluconate in 500 cc. of a 5 per cent aqueous solution of dextrose should be given intravenously in a period of not less than one hour. This solution also is administered under continuous electrocardiographic control. More than this amount usually is unsafe since conversion to sinus rhythm sometimes occurs an hour or more after the administration of the drug has been discontinued.

Quinidine gluconate or sulfate also can be administered intramuscularly. The dose is the same as the oral dose, that is, 3 gr. four times a day. The blood pressure should be taken periodically. If hypotension should develop, it can be treated by elevating the patient's legs and by administering Neo-synephrine hydrochloride.

If cardiac dilatation, congestive heart failure or pulmonary edema develops, 8 cc. of liquid Cedilanid (1.6 mg. of Cedilanid) should be administered immediately by the intravenous route, or 8 cc. of Cedilanid-D should be administered intravenously or intramuscularly.

If Pronestyl and quinidine fail to control the ventricular tachycardia, full digitalizing doses of digitalis may be employed, although the advisability of using this drug in the treatment of ventricular tachycardia is debatable. Potassium chloride, 2 gm. three times a day, may be administered orally if the tachycardia is due to an excess of digitalis.

For the prophylactic treatment of ventricular tachycardia, the oral administration of 12 gr. of quinidine sulfate daily in divided doses, or even double this amount, is satisfactory in most cases. Administration of 1.5 gm. of digitalis leaf in divided doses over a period of three to five days and the subsequent administration of a daily maintenance dose of 0.1 gm.

has been given with success in a small percentage of cases.

Ventricular Fibrillation

Ventricular fibrillation is a rapid series of inco-ordinate ventricular contractions due to a state of increased irritability of the ventricular musculature (figure 15). When persistent, it is associated with syncope as a fibrillating ventricle fails to maintain blood pressure, and, as a rule, death occurs within three minutes.

This arrhythmia may be caused by myocardial infarction, hyperkalemia, anesthesia, Pronestyl, quinidine and digitalis. It is particularly likely to occur in patients with complete A-V block.

When ventricular fibrillation constitutes an acute medical emergency, the cause should be removed, if possible, and 100 mg. of Pronestyl hydrochloride should be administered intravenously, every two minutes, under electrocardiographic control. The total dose of this drug should not exceed 750 to 1000 mg. If cardiac arrest follows the administration of Pronestyl hydrochloride, intracardiac injection of 0.1 cc. of a 1:1000 solution of epinephrine is indicated.

When ventricular fibrillation occurs in the course of an operation, oxygen should be administered by positive pressure breathing to control the respirations. A thoracotomy is performed and cardiac massage is employed. An electric shock is used, or a 2 per cent solution of procaine hydrochloride may be injected into a ventricle to cause defibrillation with cardiac arrest. The myocardium, which is in ventricular standstill, may be stimulated with an electric cardiac pacemaker or by intracardiac injection of 0.1 cc. of a 1:1000 solution of epinephrine.

Discussion

The treatment of the cardiac irregularities has been discussed from a rather dogmatic point of view in an attempt to crystallize the experience of cardiologists in the management of patients with the common cardiac irregularities. The general approach to the problem is to determine if there is an altered state of irritability of the myocardium or of the autonomic nervous system, and to correct this abnormality by the proper selection of drugs. The drugs which are employed fall into six categories. These will be discussed singly.

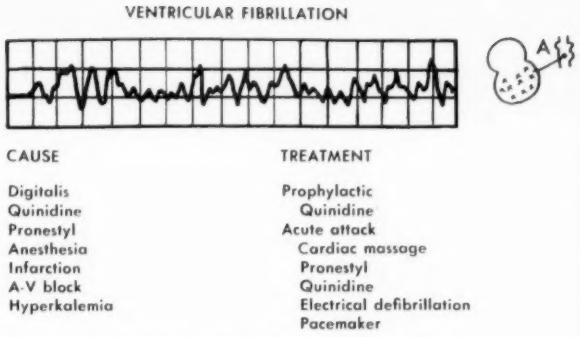


FIGURE 15. Ventricular fibrillation may result from multiple irritable foci in the ventricles or from stimulation of the adrenergic fibers of the sympathetic nervous system.

The myocardial stimulants or the drugs acting directly on the myocardium to increase metabolic activity are epinephrine, aminophylline, Norisodrine, Isuprel, caffeine, calcium salts and barium chloride. These agents have the property of producing cardiac acceleration, and they increase the excitability of the musculature and the conduction systems. They are used when there is depression of the myocardium, for example, in cases of A-V block and cardiac standstill.

The myocardial depressants are quinidine, Pronestyl, potassium and digitalis. These agents are employed when there is excessive stimulation of the myocardium, for example, with ectopic beats, auricular and ventricular fibrillation, auricular flutter, or with auricular, nodal or ventricular tachycardia.

The parasympathomimetic agents have an action similar to that produced by stimulation of the parasympathetic nervous system. They include Mecholyl, Prostigmin, STIGMONENE® (benzpyrinium bromide), morphine, veratrum viride, digitalis and digitalislike drugs, apomorphine, ipecac, reserpine and Rauwiloid. (Neo-synephrine, Levophed and Vasoxyl have a similar action which is secondary to elevation of the blood pressure, but these drugs do not belong in this class.) The parasympatho-

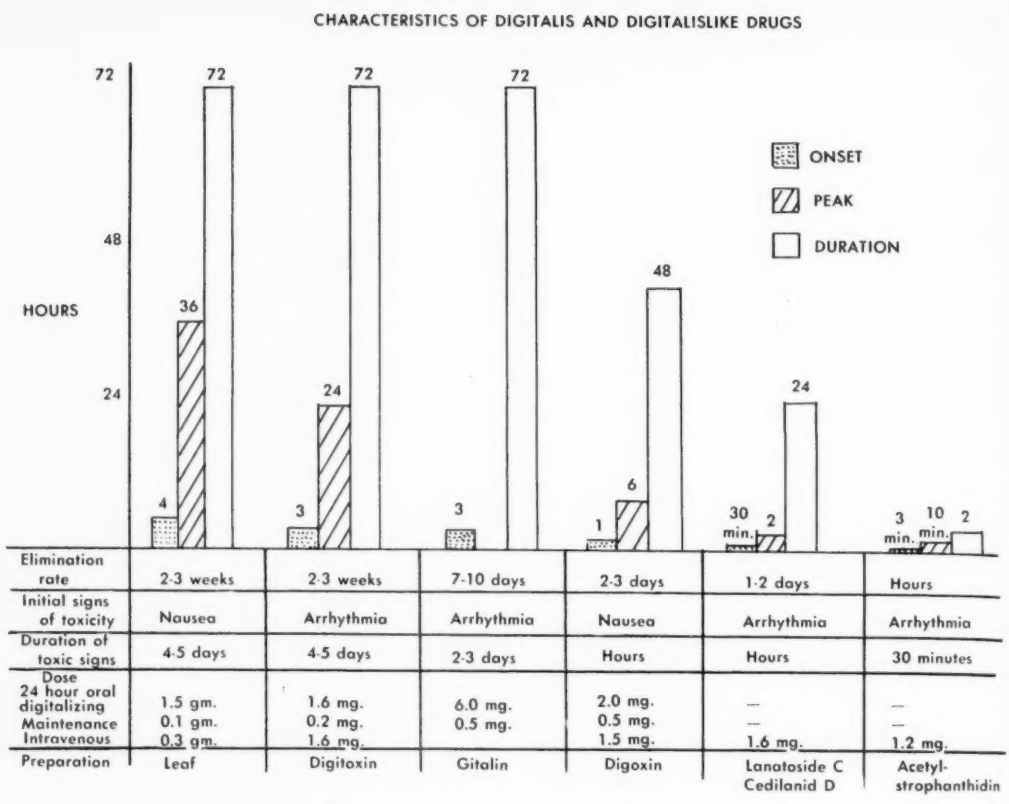


FIGURE 16. Characteristics of digitalis and digitalislike drugs.

mimetic drugs are useful in the treatment of paroxysmal auricular or nodal tachycardia. Reserpine and Rauwiloid are especially useful in the treatment of sinus tachycardia due to anxiety.

The parasympathetic blocking agents interfere with the action of the parasympathetic nervous system. They include Banthine, PROBANTHINE®, atropine and belladonna. There are many other compounds of a similar type. These agents decrease parasympathetic tone and are used in the treatment of sinus arrhythmia, sinus bradycardia, sinus arrest, and first, second, and, at times, third degree A-V block.

The sympathomimetic agents have an action similar to that produced by the stimulation of the sympathetic nervous system. These include epinephrine, ephedrine, Paredrine, Isuprel and Norisodrene. These agents are useful in the treatment of first, second or third degree A-V block.

The sympathetic blocking agents are reserpine, Rauwiloid, HYDERGINE® (dihydrogenated ergot alkaloids) and hexamethonium. Reserpine, Rauwiloid and Hydergine block centrally. Hexamethonium blocks the sympathetic and parasympathetic nerves at the ganglia. Some of these agents may be employed for the treatment of sinus tachycardia or certain types of premature contractions.

Two of the most important agents for the treatment of the cardiac arrhythmias are digitalis and quinidine. There are many digitalis

preparations available, each of which has its special characteristics concerning the onset, and duration of action, and the rate of excretion. Their actions may be short or long, and for this reason the various preparations are suitable for treatment of acute and chronic cardiac arrhythmias. A comparison of these characteristics is shown in figure 16. It can be seen that digitalis leaf and digitoxin from the purple plant are slow in onset of action, have a long duration of action, and a slow elimination rate. Acetyldigitoxin from the yellow plant and gitalin are excreted more rapidly than is digitoxin obtained from the purple plant. DIGOXIN® has a still shorter onset of action, duration of action, and excretion rate, and may be employed orally or parenterally when a quick-acting agent is indicated.

Cedilanid is a very short acting, relatively safe, intravenous preparation from the yellow digitalis plant, which is well suited for the treatment of certain acute cardiac irregularities. Cedilanid-D is employed in similar doses but has the advantage of being suitable for either intramuscular or intravenous administration. Acetylstrophanthidin acts exceedingly quickly and its duration of action is short. This agent is not yet available for clinical use.

It is important to note that certain preparations usually produce nausea as the first sign of intoxication. This provides a useful and safe means of controlling the case. All of these agents have the typical actions of digitalis, that is, they increase vagal tone, depress the myocardium, augment ventricular contractions in the failing heart, decrease the size of the dilated heart, and increase the cardiac output in the failing heart. Digitalis is indicated in auricular and nodal tachycardia, auricular fibrillation and flutter and, of course, in congestive heart failure. Toxic reactions to digitalis are treated by discontinuing the drug and by giving potassium, Banthine and, perhaps, Pronestyl.

Quinidine is available as the sulfate or the gluconate, and may be given by the oral, intramuscular or the intravenous route. Quinidine gluconate may be given by continuous intravenous drip; however, this method is rarely indicated and should be employed only by those fully familiar with this agent. The toxic manifestations following quinidine administration are idiosyncrasy, hypotension, respiratory failure, congestive heart failure, ventricular fibrillation, muscular weakness, vertigo and exfoliative dermatitis. There is no specific antidote for this agent; however, Neosynephrine, aminophylline, oxygen and digitalis may be employed as supportive therapy.

Summary

The generally accepted procedures and drugs for the treatment of the common cardiac irregularities have been discussed and evaluated in the light of the personal experience of the authors.

Endocrine Therapy in Gynecology

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WILLARD ALLEN

THE majority of my comments will pertain to the use of the sex steroids and to the endocrine problems which face the gynecologist and, also, the general practitioner.

The general principles of endocrine therapy can be summarized as follows: (1) Hormones may be used in cases in which there is a proved deficiency of a particular hormone; (2) they may be used in cases in which there is no obvious or proved hormonal deficiency if one feels that the addition of a particular hormone may be beneficial, and (3) overdoses of hormones may be administered for the specific purpose of producing alterations which may be beneficial in a particular case.

The Menopause

I shall first discuss one of the chief indications for the use of the female sex hormone, estrogen. A condition which is seen frequently and in which many of the symptoms are due to estrogen deficiency is obviously the menopause. The word menopause should probably not be used to designate anything other than what the word means, namely, the cessation of the menstrual periods. The term menopausal syndrome does not mean the presence of a menstrual disturbance; it usually indicates the presence of hot flashes and a multitude of other symptoms. In the menopausal syndrome the symptoms frequently begin to appear some years before the actual cessation of the menstrual periods. Usually, when the menstrual periods have ceased, the majority of the symptoms may be considerably alleviated. At any rate, within a year or two after cessation of the periods in the majority of patients, there are few symptoms except occasional, and usually nontroublesome, hot flashes.

In the treatment of the menopause with estrogen, there are, of course, several practical approaches. One has to decide what hormones to use and how to use them. At present, there are excellent preparations available for oral use as well as good preparations for intramuscular injection. Generally speaking, one can accomplish as much with oral therapy, provided the dose is adequate, as one can accomplish with intramuscular injection. The therapy is simpler when the hormone is given orally, and is usually just as satisfactory to the patient. In treating patients with the meno-

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pausal syndrome, the usual dose approximates the physiologic dose, which is an amount of estrogen that might normally be expected to be produced during the normal reproductive years. This is not a large dose. If one is speaking of stilbestrol, the dose seldom needs to be more than 0.5 mg. a day. Many patients will be effectively relieved of their symptoms with only 0.25 mg. or sometimes even 0.1 mg. per day. When patients require 5 or 6 mg. of stilbestrol per day, one should strongly suspect that the effect is psychic, not physiologic.

When natural estrogens are used by mouth, the dose does not need to be very great, although it should be said immediately that with most preparations at least 10 times as much needs to be given orally as is needed parenterally. In the case of sodium estrone sulfate, or perhaps I should say the preparation which contains sodium estrone sulfate and other conjugated steroids from the urine of pregnant mares, the customary dose is 1.25 mg. or less per day. An occasional patient may need 2.5 mg. daily. To pick out one preparation used intramuscularly, say estradiol benzoate, it is seldom necessary to give more than 1 mg. per week. There are now several preparations on the market for parenteral use which have a prolonged effect. These are considerably simpler to use than the shorter-acting injectable estrogens. Some of these preparations have an effect for at least three weeks, and perhaps even a month. This, of course, simplifies markedly the use of injectable material.

A word should be said about the diagnosis of the menopause. There are no laboratory tests which are genuinely beneficial. As ovarian activity declines and disappears, the follicle-stimulating hormone in the urine increases considerably. This is virtually diagnostic of ovarian deficiency. It is not, however, an indication for therapy. I need only point out that higher levels of follicle-stimulating hormone continue many years after menopause has occurred and after all the customary symptoms have disappeared. Similarly, the vaginal smear is not of particular value in determining the need for therapy. It may be quite helpful in determining whether or not a sufficient quantity of estrogen has been given to produce the normal biologic effect on the vagina, namely, full cornification. Used in that light, the vaginal smear is helpful. But, just as in the case of the determinations of the follicle-stimulating hormone, the vaginal smear many years after the menopause indicates estrogen deficiency, but the symptoms have all disappeared; hence no therapy is indicated.

Atrophic Vaginitis

There are two instances, one in childhood and the other in the postmenopausal state, in which, in the absence of any of the usual menopausal symptoms, it may be desirable to use estrogens. I refer to the atrophic vaginitis which is seen in elderly women and occasionally in childhood. Formerly, we used to suppose the vaginitis in children was specific, that is, due to *Neisseria gonorrhoeae*. This, nowadays, is seldom the case, but in many children vaginitis still develops because of contamination of the vagina by stools and urine and occasionally even by foreign bodies.

It is very simple to treat vaginitis in children. This can be done by the use of vaginal suppositories, and, in some cases in which this does not seem feasible, it is quite easy to insert with a medicine dropper a few drops of any oily solution containing estrogen. The amount can be quite small, 2 or 3 drops per day for about two weeks. Usually, the vaginitis disappears promptly. In the postmenopausal women, the simplest procedure is to use suppositories, usually stilbestrol suppositories containing 0.5 mg. each. In the elderly women, estrogen given vaginally this way is frequently quite helpful in treating urethral caruncle. The estrogen stimulates the lining of the vagina and, at the same time, causes the caruncle to be covered over with more normal vaginal epithelium. This, obviously, is not the procedure in cases in which there is a large caruncle. These patients should be treated surgically.

Overdosage of Estrogens

Next, I would like to make a few comments about deliberate overdosage with estrogen. Are there any situations in which anything is to be gained by overdosage? The answer to this is that there are at least two, and possibly

three such situations. Whenever one uses overdoses of estrogen, spontaneous ovulation is abolished. This effect is mediated by way of the pituitary body because large quantities of estrogen suppress the output of follicle-stimulating hormone and hence interfere with the processes of ovulation.

One of the simple excuses for using estrogen in this way is to be found in essential dysmenorrhea. The administration of overdoses of estrogen, beginning about 10 days before the expected onset of ovulation, will almost invariably suppress ovulation. Practically, this means that if one gives 5 or 6, maybe 10 mg. of stilbestrol per day by mouth for about three weeks, beginning at the third or fourth day of the menstrual flow, the next period will occur about one month after the last period. This period, however, occurs because of withdrawal of estrogen and is in every sense of the word an artificially induced period. Surprisingly enough, the induced period is frequently not accompanied by cramps.

The old saying that essential dysmenorrhea means an ovulatory cycle is still true. This obviously is not a method to be used indefinitely for the treatment of dysmenorrhea, but is a method which can be used on special occasions to abolish a painful period, when for good reason the person wishes to have a relatively painless period. There is no real harm in this procedure since on discontinuance of the use of estrogen, after two or three cycles, normal ovulation is resumed. Usually, dysmenorrhea reappears with the first ovulatory cycle.

Another instance in which overdosage with estrogen is helpful is in patients with prolonged functional uterine bleeding. The estrogen in this instance, surprisingly enough, stops the bleeding after a few days in most cases. At the same time, it induces ovarian deficiency. When the administration of estrogen is discontinued after about three weeks, withdrawal bleeding usually occurs, and, following this, normal cycles may be resumed. This therapy does not in any way alter the basic abnormality which induced the failure of ovulation and the functional uterine bleeding. In these two examples of overdosage with estrogen, the amount necessary is approximately 5 to 10 times the physiologic dose. In terms of stilbestrol, this being the hormone most frequently used for this purpose, the dose does not need to be more than 10 mg. per day. In most cases, 5 mg. daily will suppress ovulation.

There is another rather paradoxical use for stilbestrol. This is in the treatment of endometriosis. Stilbestrol, as pointed out originally by Karnaky, when given in gradually increasing amounts so that after two to three weeks of medication the daily dose is approximately 100 mg., does decrease the painful symptoms associated with this disease in a high percentage of cases. The general rule is that the therapy should be continued for three to six months. During this period, there may be pigmentation of the nipples and areolae in many cases, some enlargement of the uterus, and frequently a little pinkish, even bloody, vaginal discharge. This bleeding is an indication of induced hyperplasia of the endometrium.

Karnaky feels that the nodules may disappear. It seems, however, that in many cases there is no palpable difference in the size of endometrial implants in the uterosacral ligaments or cul-de-sac, and, certainly, in enlarged ovaries due to endometriosis, there is not much change. The beneficial results are presumably brought about by increased vascularity of the pelvic structures which produces a loosening of adhesions if they are present, and perhaps, the good results may be due to the suppression of the progestational phase in the endometrial implants. Stilbestrol, when used for the treatment of endometriosis, undoubtedly completely suppresses ovarian activity. This eliminates progesterone and hence eliminates the periodic growth resulting from the production of progesterone in the ovulatory cycle.

I should say that, in my own opinion, endometriosis can frequently be corrected fairly effectively by conservative operations if they are not postponed too long. The use of stilbestrol, it seems to me, finds its place in patients in whom the diagnosis is relatively certain and in whom one would not wish to go to the extreme of removing the ovaries as a means of quieting the growth of the endometriosis. Surprisingly enough, many patients treated with stilbestrol remain relatively symp-

tom free for many months after the resumption of normal cycles. In fact, a few such patients have had children.

Progesterone

I now come to a discussion of the uses of progesterone. Progesterone is produced during the second half of the normal cycle and produces the progestational changes which occur in the endometrium and which make implantation of the embryo possible. This leads immediately to the question of the use of progesterone in the treatment of abortion, either threatened or habitual, and possibly also in some cases of infertility in which the endometrium may not be adequately prepared for satisfactory implantation of the embryo.

The frequency of abortion is probably at least as high as 10 per cent in all pregnancies. Every obstetrician knows that the majority of all such miscarriages occur as a result of defective development of the embryo. At least one can say with some certainty that in most spontaneous abortions the fetus is either absent or, if present, has certainly not developed anywhere near the size which it should have developed for the period of gestation. Obviously, the use of progesterone or any other hormone for the prevention of abortion in these cases is completely contraindicated.

Unfortunately one cannot always tell by examining a patient who is bleeding and threatened with a miscarriage whether or not the embryo is normally developed. In most cases, one cannot speak with any degree of certainty to this point. In some instances, it is relatively obvious from examination that the uterus is smaller and more firm than it should be for the period of gestation. In these cases, it is certainly unwise to try to prevent the completion of the miscarriage by natural methods.

Secondly, there is very little evidence on hand at the present time to indicate that abortions of normal embryos occur because of progesterone deficiency. On the other hand, it is well known from experiments on animals that the removal of the ovaries, which are the source of progesterone, almost invariably leads to miscarriage. In the rabbit, removal of the ovaries leads to resorption of the embryos in the early stage of pregnancy, or to premature delivery if removed later in the pregnancy. There is a great temptation to transfer this information obtained by experiments on animals to the human being with the expectation that progesterone would be quite effective in the prevention of miscarriage. Unfortunately, administration of progesterone to the patient threatened with a miscarriage probably has little real effect.

There are other cases, much more rare to be sure, in which pregnancy terminates habitually before viability. In these cases, the patients can be categorized as having habitual miscarriage or habitual premature labor. In many of these patients the embryos are normally developed. My own feeling about the treatment of such patients is that if one is to use progesterone its administration should be begun well before the expected time of miscarriage or premature labor. Also, the dose should be considerable. The amount of progesterone produced during normal pregnancy is not known directly. One would suppose, however, from the amounts of pregnanediol excreted during pregnancy, that the production of progesterone by the mother in early pregnancy may be 40 to 50 mg. per day and toward the end of pregnancy perhaps 200 or 300 mg. per day. It seems logical, therefore, to give substantial amounts of progesterone if one expects to obtain any physiologic activity from it.

The difficulty in using progesterone is that it is a rapidly metabolized compound, and hence it really should be given every day. Likewise, progesterone is not very soluble in sesame oil, the usual agent used for the solution of the progesterone. To give 200 mg. per day of a solution containing 50 mg. per cubic centimeter obviously requires the injection of 4 cc. per day. Whether or not one can accomplish much with 50 or 100 mg. per day is not at all certain. There is one additional point that needs to be mentioned, however, namely, that in patients who have repeated miscarriages the likelihood of spontaneous cure is considerable until a patient has had at least three spontaneous miscarriages. In fact, one can say that four consecutive miscarriages are required before one can appraise the effect

of a hormone such as progesterone.

In treating habitual abortion and habitual premature labor, one inevitably must think about the use of stilbestrol. Stilbestrol, as you know, has been recommended for use during pregnancy. It is undoubtedly not dangerous, but it is highly dubious whether or not stilbestrol really has any beneficial effect on such complications as bleeding and premature labor which occur during pregnancy. I do not mean by this, of course, that one should not use stilbestrol at all. In patients who have bad obstetric histories of this sort, one is tempted to use almost anything, in fact, is almost forced to use something in the hope that at least one pregnancy will go to term.

There are other uses of progesterone which are well established and which are genuinely beneficial. There are two conditions in which ovulation fails to occur, hence in which there is no production of progesterone. These conditions manifest themselves either as functional uterine bleeding or as secondary amenorrhea. Both of these are usually due to failure of ovulation. First, speaking of functional uterine bleeding, especially the kind that is seen in females less than 20 years of age, the usual history is that the periods initially may have been regular, but then amenorrhea appears. After a short period of amenorrhea, bleeding begins and may occur sporadically or even continuously for weeks or even months. Endometrial biopsy usually shows an interval type of endometrium or cystic hyperplasia.

The administration of progesterone for a few days is promptly followed by desquamation of the endometrium. This is called chemical curettage, because, when the administration of progesterone is discontinued, bleeding and desquamation of the endometrium follow within two or three days. There are several ways of giving the progesterone. One is to give 10 mg. a day for six days; another, to give 25 mg. a day for three days; and another, to give 50 to 100 mg. in a single dose. Progesterone can also be used buccally, although this is not quite as satisfactory as giving the hormone by injection. The buccal dose is from 50 to 100 mg. per day for five or six days. In some cases, it is desirable to give estrogen for two weeks prior to the progesterone.

Also, there are some preparations on the market in which the progesterone is combined with estrogen. These are all equally effective. I think it can be said with considerable certainty that progesterone is quite satisfactory in the treatment of functional uterine bleeding in most cases in which the patients are in the younger age group. In the older age group, that is, those approaching the menopause, the hormone exerts the same effect and is equally beneficial. In the menopausal or premenopausal patients who have functional bleeding, spontaneous cures do occur; however, it is necessary to do an endometrial biopsy and a biopsy of the cervix to find out more specifically what may cause bleeding, because in this age group cervical cancer, endometrial cancer and benign tumors may be responsible.

In secondary amenorrhea, in which the ovaries are producing a moderate amount of estrogen, the injection of progesterone according to the schedule just outlined for use in functional uterine bleeding is completely satisfactory. Almost invariably, a menstrual period will occur as a result of the withdrawal of progesterone, and menstrual periods frequently will occur spontaneously afterward.

There is one additional aspect to the use of progesterone in secondary amenorrhea. It serves as a very good test for the production of estrogen by the ovaries. Progesterone exerts little or no effect on the endometrium in the patient whose ovaries are not producing estrogen. Consequently, when progesterone is given in adequate doses and withdrawal bleeding does not occur, one immediately suspects that the ovaries are producing little or no estrogen. The procedure is simple. One tests the capacity of the endometrium to break down following progesterone withdrawal without the prior administration of estrogen. If bleeding fails to occur, then estrogen is given for about three weeks, and in the last few days of this period, progesterone is given intramuscularly. Here, withdrawal bleeding usually occurs.

I also should mention that an occasional patient in the younger age group who has secondary amenorrhea and fails to respond to this scheme for the testing of estrogen produc-

tion and the capacity of the endometrium to break down following withdrawal, should be curetted because some patients who have failed to respond to progesterone under presumably ideal circumstances are found to have tuberculosis of the endometrium. The failure of bleeding to occur in patients with tuberculosis of the endometrium is not necessarily due to ovarian dysfunction. Bleeding may not occur because the endometrium is so altered by the tuberculosis that it is not capable of breaking down on either estrogen or progesterone withdrawal.

I would be somewhat remiss if I did not mention that hormone therapy in secondary amenorrhea and in functional uterine bleeding may not be the answer to the problem. The basic cause for the failure of ovulation, regardless of whether the patient has functional bleeding or secondary amenorrhea, is frequently not known, nor is it possible at the present time to determine why ovulation is not occurring. This brings up the question of what factors do lead to ovarian deficiency prior to the normal time of the menopause. It is well known that some patients with functional disturbances of ovarian activity may have hypothyroidism. Other patients may be in poor general health; other patients may be anemic, and some patients may have combinations of all these factors. It is not illogical to use "shotgun" therapy as a means of stimulating ovarian activity, the therapy consisting of thyroid, vitamins, and, sometimes, iron. In this same connection, one might also mention that there is an occasional patient with protracted uterine bleeding who has thrombopenic purpura and in whom the only manifestation of the disease is excessive menstrual bleeding.

Estrogen-Androgen Therapy

I now come, in conclusion, to a discussion of a somewhat different but related problem. This is the use of estrogen and androgen therapy, and also the use of androgens. Overdosage with androgen suppresses ovulation in much the same way as overdosage with estrogen does. The real objection to using male sex hormones for this purpose is that this hormone is virilizing. I think that, as time has gone on, less and less male sex hormone is being used for gynecologic endocrine problems. This cannot be said, however, with reference to the combination of male sex hormone and female sex hormone. There is little doubt but that estrogen by itself is much more effective in controlling symptoms of the menopause than is androgen. However, one of the real objections to the use of estrogen in menopausal and postmenopausal patients is that the prolonged use of estrogen almost invariably leads to bleeding. It behooves the doctor to realize this bleeding does not mean cancer.

It is very simple to find out without detailed diagnostic procedures whether or not the bleeding is related to the sex hormone that is being administered. All that is necessary is that the administration of estrogen be discontinued, and, in practically every case in which the bleeding is due to the estrogen, it will stop in approximately two weeks. If bleeding continues beyond two to three weeks, one then should certainly do at least a suction biopsy in the office and more probably a complete curettage. The reason that androgen has been added to estrogen in treating menopausal and postmenopausal patients is that androgen to a certain extent is antiestrogenic, and it improves the patient's vigor probably much more completely than does estrogen. Patients receiving androgens go into positive nitrogen balance. This can be reflected in better health.

The combination hormones are, therefore, placed on the market with the idea that they can be used for the better treatment of menopausal and postmenopausal patients, the androgen supposedly reducing the bleeding tendencies from the estrogen, and the estrogen, in turn, reducing the virilizing properties of the androgens. Whether or not this is a completely safe and sane interpretation of the reasons for the combination I cannot say, nor can I say that the combination behaves as it is supposed to. The fact remains, I think, that this combination therapy is being used extensively. I do not believe there is any real danger in the use of this mixture, but it certainly is not a preparation that one should give to a patient and have her take indefinitely without being seen periodically by the physician.

The Care of the Seriously Ill Asthmatic Patient

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THE patient with severe asthma may require prompt treatment if disastrous consequences are to be avoided. Although most patients respond rapidly to therapy, an occasional patient will respond slowly or not at all. It is particularly toward the care of such refractory asthmatic patients that these remarks are directed.

In the management of asthma, there are certain objectives which one wishes to achieve. First, one wishes to control the environment of the patient who is acutely ill with asthma. Next, one wishes to bring about relief of the troublesome symptoms the asthmatic patient is experiencing. The third objective is one of controlling the complications of asthma and those coexisting diseases which are influencing the severity of the patient's distress.

Control of the Environment

In the matter of controlling a patient's environment, it is most desirable that hospitalization be considered. This is particularly true for the patient who is seriously ill with asthma and who is responding poorly to measures which have been introduced for his care in the home. A hospital room immediately removes the patient from contact with rugs, draperies, dust, respiratory irritants and other offending allergens which may be present in his home. When possible, dustproof covers should be applied to the mattress and pillows of the hospital room prior to the patient's arrival. Kapok should be avoided as a substitute for feathers because patients frequently are allergic to it. Foam rubber pillows and mattresses are satisfactory for most allergic patients. Sweeping should be avoided in the

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room, since it resuspends dust in the air. Floors should be cleaned with a damp cloth. The better control of humidity and of temperature in the hospital greatly favors healing of bronchitis. During seasons when pollens to which a patient may be sensitive are in the air, a pollen filter should be placed in the hospital window to permit only pollen-free air to enter the room. Obviously, doors, transoms and other means by which pollen-laden air might enter a room should be kept closed.

My colleagues and I prefer to place the patient with asthma in a private room. In a ward it is most difficult to control cosmetic preparations of other patients, dust and pollen. Asthmatic patients often have their greatest trouble during the night. This engenders in other patients an apprehension which is very contagious. Another advantage of hospitalization is that of getting a patient away from overly anxious and solicitous relatives.

Many measures introduced into the therapy of asthma are more readily available in the hospital than in the home. Such measures include the inhalation of therapeutic gases, the use of parenteral fluids, and the prompt administration of injected medications. If, however, hospitalization is not available, many therapeutic measures can be adapted to use in the home.

Production of Symptomatic Relief

Patients who are in the throes of an attack of asthma require prompt attention. If medication to relieve asthma is administered early, the total amount necessary usually is less. Conversely, if one allows an attack of asthma to become well advanced without instituting therapeutic measures, more medication is then necessary.

Bronchodilators—First in measures for symptomatic relief, I should like to consider the use of bronchodilators. The most effective of these is epinephrine. My colleagues and I commonly use it in an aqueous solution, giving from 0.25 to 0.5 cc. hypodermically. We prefer the repeated use of smaller doses of epinephrine at 20 minute intervals to the occasional use of larger injections. The timid and inadequate use of epinephrine probably has been the basis for more disastrous results in the treatment of asthma than has the excessive use of this drug. Epinephrine should be used in smaller and less frequent doses in those patients who present the relative contraindications of old age, vascular disease and hypertension. It is true, however, that when such patients have severe asthma they may suffer more trauma from the struggle with asthma than they might from the epinephrine which would effectively afford relief. Individual variation in patient response may permit smaller doses in certain subjects.

We prefer the use of epinephrine in aqueous solution to that dissolved in oil. Such vehicles prolong the duration of its effect but permit the absorption of epinephrine at times when it may be less urgently needed. Also they curtail the absorption of the drug at times when the need for it is great.

Certain chronically ill patients may need to have repeated injections of epinephrine over a prolonged period. It is desirable to instruct such patients in the self-administration of this drug. Patients who can inject epinephrine meet the onset of an attack of asthma with far more confidence when not depending on another person for this service.

Certain patients may derive benefit from a nebulized bronchodilator to permit early and readily available treatment for asthma. Two types of solutions are widely used. One consists of epinephrine in solutions of 1 to 3 per cent. More recently another similar substance has been introduced. This is isopropylnorepinephrine, which manifests fewer cardiovascular side effects than epinephrine while retaining its asthma-relieving property. Isopropylnorepinephrine is available for nebulization in a 0.5 and a 1 per cent solution. Likewise this material may be given by sublingual use in a tablet form. It is also available as a powder for use by insufflation. It should not be injected. The relief produced by epinephrine and by isopropylnorepinephrine is prompt though transitory.

Another important group of bronchodilating drugs for the management of asthma is ephedrine and similar drugs. These induce a moderate epinephrinelike effect which is pro-

longed over a period of four to six hours. Ephedrine likely owes its effectiveness to its capacity to slow the rate of enzymatic destruction of endogenous epinephrine. The usual dose of ephedrine sulfate is ⅜ gr. (0.024 gm.) administered orally at intervals of four hours. For some patients ephedrine may be contraindicated because of undue cerebral excitation or cardiovascular symptoms which occur following its use. In elderly men who have a degree of urinary obstruction the use of ephedrine may accentuate this problem.

If the patient's tolerance for ephedrine is poor, there are other ephedrinelike drugs such as methoxyphenamine hydrochloride (ORTHOXINE®) or phenylpropanolamine hydrochloride (PROPADRINE®) which are useful. Their side effects are fewer than are those of ephedrine. However, their influence on asthma is also somewhat less.

Among the xanthine derivatives, aminophylline is the most important in the management of asthma. This drug is most effective when administered intravenously. My colleagues and I employ doses of 3¾ to 7½ gr. (0.25 to 0.5 gm.) in each liter of the intravenous fluids used initially to hydrate the asthmatic patient. In the occasional critically ill patient it may be necessary for a more concentrated aminophylline solution to be administered directly into the vein. If this is necessary, one should use a 3¾ gr. (0.25 gm.) dosage in at least 10 cc. of diluent, and the drug should be administered very slowly. Aminophylline given by oral administration and that administered rectally are somewhat helpful in reducing the severity and frequency of milder nocturnal asthmatic attacks. Aminophylline suppositories containing 7½ gr. or similar amounts of the drug dissolved in tap water may be administered rectally for a prolonged antiasthmatic effect. The influence of such rectal medication extends over perhaps an eight hour period. In certain patients rectal or perianal irritation develops, precluding the further use of aminophylline by this route.

Gas inhalation therapy—For the therapeutic administration of gases to the asthmatic patient my colleagues and I prefer to use the BLB mask. There are reasons for this preference. Such a mask may be applied or removed more easily than a nasal catheter or an oxygen tent in accordance with the varying needs of the asthmatic patient. For a seriously ill asthmatic patient in whom continuous oxygen therapy is necessary, an oxygen tent may prove more suitable than the mask.

The gases which we most often employ in inhalation therapy are oxygen or oxygen diluted with helium. Helium has a unique physical property of flowing with ease through constricted passages such as narrowed bronchi. A mixture containing 80 per cent helium and 20 per cent oxygen is available for administration and may be given directly. However, we usually administer such a helium-oxygen mixture diluted with an equal part of oxygen alone. In either event a flow of 6 to 9 l. a minute usually affords symptomatic relief. One should ensure that the rebreathing bag of the BLB mask is not completely emptied at the end of inspiration. Although gas inhalation therapy does not relax bronchospasm, it does enable the patient to breathe more easily. The patient's voice will assume a high-pitched character during the time that the mixture of helium and oxygen is being administered. This occurs because of the vibration of vocal cords in a less dense gas. Unless patients are so advised they are likely to become alarmed.

The occasional patient who has advanced pulmonary emphysema may be adversely affected by oxygen therapy. In such individuals a degree of oxygen want affords a critical stimulus to the flagging respiratory center. The sudden change afforded by oxygen therapy often may allow a depression of the respiratory center, causing apnea and unconsciousness. When such a condition exists, one must reduce substantially the amount of oxygen used, retaining only that which will afford some relief but which still does not remove a critical stimulus that oxygen want affords.

In recent years there has been considerable interest directed toward positive-pressure breathing devices such as the Bennett valve and the Mine Safety valve. While an occasional patient seems to derive benefit from the use of these, most asthmatic patients prefer not to use such machines. It is of interest,

however, that asthmatic patients commonly provide a measure of positive pressure by exhaling against partially closed lips. The principal usefulness of permitting positive-pressure respiration devices is in those patients having an element of pulmonary edema.

Another gas which my colleagues and I use in the management of asthma is carbon dioxide. This is particularly helpful in that group of asthmatic patients which has recently undergone upper abdominal operations. Operations on the stomach, kidneys, diaphragm, colon or biliary passages are likely to bring about splinting of the diaphragm. This predisposes the asthmatic patient to atelectasis. Following operation on asthmatic patients we often employ gas therapy in the form of 5 per cent carbon dioxide in 95 per cent oxygen as a respiratory stimulant. Periodic inhalations of this gas mixture will effect better aeration of the lungs and thereby reduce the incidence of postoperative atelectasis.

Adequate hydration—It is of paramount importance to bring about adequate hydration of the seriously ill asthmatic patient. Such patients have often eaten poorly, have consumed small quantities of liquids and through perspiration and through vaporization from the lungs have lost large quantities of liquid. Fluids should be administered until normal hydration has again been established. When the seriously ill patient is admitted to the hospital, intravenous therapy is begun without delay. Fluids are administered continuously until a total of 2 to 3 l. has been given. A 5 per cent solution of dextrose in water usually is suitable. For those patients receiving cortisone or corticotropin, it may be especially desirable to omit all sodium in the injected fluids. The dextrose administered in fluids provides nourishment and also replenishes the glycogen of the liver. Such patients have had numerous injections of epinephrine which have served to deplete glycogen stored in that organ. Later the administration of intravenous fluids is limited to twice daily. One liter is given in the morning and the second preferably in the evening. Aminophylline is usually added to these fluids. In addition to the parenteral administration of fluids, the asthmatic patient should drink copious amounts of liquid. My colleagues and I encourage such individuals to drink a glass of water every hour during the daytime. As oral hydration improves, one can decrease and ultimately discontinue the use of fluid administered parenterally.

Certain patients who are seriously ill may have an element of congestive heart-failure as a contributing factor in their illness. We curtail the hydration of such patients until it is clear that the cardiac reserve is adequate to handle the quantity of fluid which we customarily administer.

Expectorants—One of the most helpful drugs, yet a drug too often omitted from the therapeutic regimen for a patient having asthma, is an appropriate expectorant. The principal effect of such drugs is to thin the tenacious sputum. Until hydration has been produced, the value of expectorants is limited. By hydration plus the effective use of expectorants, the asthmatic patient may substantially reduce his coughing. This, in turn, reduces bronchial irritation and bronchospasm.

My colleagues and I find the most effective expectorant to be an iodide salt. We commonly use potassium iodide. This may be administered as long as tenacious secretions are being raised. With subsidence of bronchitis, the use of iodides is reduced and ultimately discontinued. Iodides are tolerated best after meals and when liberally diluted with water. Unfortunately, some patients have a poor tolerance for iodides. An acnelike eruption, swelling in the salivary glands, or other evidences of intolerance develop. Patients should be advised regarding the possibility of these intolerances. When minor intolerances occur only after prolonged use, iodides often may be employed in intermittent brief courses, the drug being discontinued before the anticipated day of difficulty. If iodides are so poorly tolerated that their use becomes impractical, one must substitute other expectorants such as ammonium chloride. However, these are less effective than iodide salts.

Recently a detergent solution for use by nebulization has been introduced. Such a solution is occasionally helpful in freeing tena-

cious secretions. Many patients find detergent solutions to be irritating, however, and only a relatively small number of patients prefer to use them.

Sedatives—The judicious use of sedatives is helpful in bringing relief from the anxiety so commonly experienced by the asthmatic patient. Through loss of sleep, mounting fear and repeated paroxysms of asthma, a state of utter physical and emotional exhaustion is likely to develop. Such a state perpetuates asthma.

When selecting a sedative one must avoid those drugs which significantly depress the respiratory center. By and large, asthmatic patients tolerate sedatives poorly. Drugs which are administered for sedation often have a stimulating effect on asthmatic patients. When sedatives are necessary my colleagues and I most commonly employ small doses of barbiturates. Chloral hydrate or chlorpromazine, however, is also useful, especially for those who are stimulated by barbiturates or in other ways tolerate them poorly.

The practice of giving opiates to the asthmatic patient is to be condemned. These drugs depress the respiratory center powerfully. Their use at a time when the respiratory function is already burdened with severe asthma is often a prelude to disaster. At no time should morphine, codeine, DEMEROL®, DILAUDID®, or similar opiate drugs be given to the patient who has asthma. By way of sedation in certain women who are having menopausal symptoms the use of estrogens is at times helpful. Antihistamine drugs usually do not play a prominent role in the management of asthma. If used, the sedative effect of certain antihistamine drugs may be helpful.

Cortisonelike drugs and corticotropin—Since the introduction of cortisone and of corticotropin the physician has had powerful weapons in the management of asthma. These drugs are useful, however, only within a rigid framework of qualifying circumstances. They are only one of several facets in the management of the seriously ill asthmatic patient. These hormones will usually control asthma effectively and rapidly. Unfortunately, this control lasts only a few days or weeks after hormone therapy has been discontinued. Asthma usually recurs unless other measures to remove or control its causes and complications are undertaken. The average duration of benefit to the asthmatic patient after discontinuation of therapy with cortisonelike drugs or corticotropin is about three weeks. Patients who get prolonged relief are those who have been able to control the factors causing their asthma.

The use of cortisonelike drugs and of corticotropin in the management of asthma has several major disadvantages. Particularly to be considered is the atrophic change which may occur in the adrenal glands after administration of cortisone and similar drugs. Patients who have a degree of adrenocortical insufficiency tolerate stress poorly. Since asthma is a disease involving periodic severe stress, it is evident that any suppressive influence on adrenocortical activity is best avoided. Other contraindications to steroid therapy are valid with the asthmatic patient as well as with patients having no asthma. Until a patient's general condition has been adequately studied it is inadvisable to use such hormone therapy.

One may use cortisonelike drugs and corticotropin for the critically ill patient when there is insufficient time to assess the influence of more conservative remedies on the patient's asthma. Also one may use these hormones for patients who are seriously ill and who are failing to respond satisfactorily to other measures employed in their relief. My colleagues and I often use cortisone in sustaining asthmatic patients who are undergoing severe stress and who have been receiving cortisone at the time they have been brought under our care, or who have used cortisone extensively in the past. Here we are more concerned with affording a crutch to adrenocortical function than we are with the therapy of asthma. Occasionally, we are called on to use cortisone or similar drugs when there is great urgency in the preoperative control of asthma, as with a patient suspected of having a malignant disease.

In using cortisone to treat asthma we prefer periodic discrete courses of therapy. These usually have extended from 7 to 22 days. Our initial daily dose is usually 300 mg. We con-

tinue with 200 mg. daily until improvement is definite, and then administer 100 mg. daily until convalescence is well established. In the final few days of therapy the dosage is gradually tapered. These daily doses are divided into four parts and administered orally at six hour intervals. Even though a later daily dose of cortisone may be small, we still divide it into four parts. For those patients who are critically ill, and for those patients undergoing operative procedures, we may supplement or replace orally administered cortisone with injected hormones. If cortisone is injected, it must be remembered that its absorption is quite slow, extending over two to three days. When the use of such medications has been prolonged, the period of tapering should be more protracted. At times it may be necessary to give repeated brief courses following the cessation of a prolonged course. In only an occasional patient have we found it necessary to employ continuous cortisone therapy for the relief of asthma.

To institute steroid therapy rapidly we may employ this program. In the fluids administered intravenously we have often given 100 mg. of hydrocortisone in a period extending over perhaps four hours. As the injection is completed we administer either cortisone, hydrocortisone or prednisone. When prednisone is used we have used doses of 10 mg. every six hours. With improvement this dose is tapered to 5 mg. every six hours and ultimately discontinued.

In using corticotropin we have administered aqueous solutions of the drug intravenously over several hours with a dose of 20 mg. Such daily injections are administered with somewhat smaller doses of corticotropin as improvement continues. More recently we have used gels containing corticotropin, giving such patients 20 to 40 mg. daily by intramuscular injection. We have divided this daily dose into two portions administered 12 hours apart. Here, too, we would prefer brief discrete courses to continuous therapy.

Objectionable measures—The use of certain drugs is best avoided in the management of asthma. Opiate drugs should be avoided because of their suppressive effect on the respiratory center. The use of burning stramonium powders and "asthma cigarettes" is objectionable. While it is true that a patient may derive relief from his asthmatic paroxysm by inhaling smoke from such burning powders, it is also true that bronchitis is perpetuated, owing to the irritation engendered by such therapy. Preparations which contain arsenic should be avoided because of the hazard associated with this heavy-metal intoxication.

Control of Complications of Asthma

Bronchitis—Among the complications of asthma, one should first speak of bronchitis. Each patient with asthma has some degree of bronchitis. Although bronchitis is first being specifically considered at this point, actually, much of what has already been discussed bears directly or indirectly on it. After upper respiratory infections, patients may raise sputum which is purulent, as evidenced by its yellow or green color. Those patients with purulent bronchitis should receive an appropriate antibiotic drug. My colleagues and I most commonly employ penicillin, the tetracycline group or erythromycin. The patient should be carefully questioned in respect to drug allergy. Asthmatic patients commonly become allergic to drugs, especially penicillin. Cultures of sputum with antibiotic sensitivity studies on predominating organisms are useful, especially with those problem patients whose asthma is difficult to control.

In addition to the oral and parenteral routes for antibiotic drug administration, one may nebulize antibiotics. To do this we commonly employ penicillin, giving asthmatic patients 200,000 units throughout the course of the day. Solutions containing 20,000 to 50,000 units per cubic centimeter of physiologic saline solution may be employed for nebulization.

There are measures which serve to reduce coughing effectively and thereby enable a more rapid healing of bronchitis. We would greatly prefer to avoid the use of drugs, such as codeine, which suppress or eliminate the cough reflex. Unless patients are raising copious amounts of sputum, we encourage them to suppress their cough voluntarily in order to eliminate all but useful coughing. Healing of

the bronchial mucosa is enhanced by the rest afforded. Of course, tobacco smoking should be eliminated. No patient who has asthma should smoke.

Bronchostenosis—A common complication of asthma is bronchostenosis. Here an area of localized inflammation occurs, usually in a tertiary bronchus of a lower lobe, with resulting edema and cicatricial narrowing of the bronchial lumen. When such a condition exists, the patient will cough excessively in a futile attempt to dislodge mucus trapped behind the stenotic area. The presence of bronchostenosis is suggested by a persisting cough associated with the suppression of breath sounds usually over a middle or lower lobe of the lung. Blood-tinged sputum often is associated with bronchostenosis. Hemoptysis does not occur in cases of uncomplicated asthma. Patients with bronchostenosis often develop a "sputum-retention syndrome," with chills and fever, usually terminated by expectoration of copious purulent sputum. If bronchostenosis is suspected, a bronchoscopic examination should be considered when the problem of acute asthma has been brought under control. If an area of bronchostenosis is found, the endoscopist can dilate it, bringing considerable relief.

Pulmonary emphysema—Many patients with bronchial asthma, as well as others having conditions associated with a cough, develop an element of pulmonary emphysema. Therapeutic measures are directed toward the eradication of bronchitis and of asthma rather than with the hope of reversing the element of pulmonary emphysema.

Miscellaneous measures—With the subsidence of the acute phase of asthma one has more latitude in evaluating the basic causative factors in the problem of asthma. At this point an otorhinolaryngologist should see the patient in order to determine if chronic disease exists in the paranasal sinuses. If such a disease actually does exist, those measures necessary to eradicate it should be undertaken. It is probable that chronic sinus infection is an important factor in aggravating asthma. The spread of infection along contiguous mucous membranes serves to ignite the inflammation in the bronchial mucosa. One may now consider an allergy survey, which likely has been deferred because of the patient's illness and the urgency of continuing drugs which might interfere with skin tests. Emotional factors which may be important may now be given more adequate evaluation.

Comment

In conclusion I should like to point out that the asthmatic patient has an illness greater than its allergic aspects. He often has many problems apart from his difficulty with asthma. Any program of treatment should have regard to the whole patient, taking into consideration asthma, its complications, other organic diseases, and the patient's emotional difficulties. Only if all of these are considered can the most effective therapy be administered.

The Study of the Sterile Couple

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THE inability to have children is of serious concern to a fairly large segment of our population. It has been estimated that about 15 per cent of marriages are barren and that in at least 10 per cent of these the failure to have a baby is of sufficient concern that the couples consult a physician. The initial medical contact is extremely important in the ultimate prognosis, for far too often the family doctor contributes little to unraveling the cause of the infertility. Indeed he may unwittingly decrease the patient's chances to have a baby by postponing indefinitely an adequate sterility investigation.

Most couples assume that the failure to have children is primarily the result of infertile women. However, the truth is that the causes of infertility are about equally divided between husbands and wives and it is important that the physician investigate the couple. A good beginning is to interview both husband and wife and to explain to them the simple and interesting facts concerning the physiology of reproduction, to outline the various procedures that will be carried out in a comprehensive sterility investigation and to emphasize that their cooperation is of the utmost importance to a successful result. Such an interview will lay the groundwork for an understanding patient-physician relationship and will decrease the likelihood that the couple will seek another physician if the wife does not conceive promptly. The endless "shopping around" for the medical man who will conjure a baby out of thin air has been the undoing of many infertile couples who would

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have had a baby had they remained under the continuous supervision of a competent physician interested in the study of sterility.

There has been considerable academic discussion as to when a couple is to be considered infertile and a study instituted. Present philosophy holds that an investigation is warranted whenever the patient consults her physician because she has not conceived. At least one can ascertain that the reproductive organs are anatomically and functionally normal. One can reassure the patient and discuss with her some of the fundamental facts concerning fertility.

Human fertility depends on many factors other than the sex organs, and too little knowledge is available concerning these factors. Age, health, nutrition and mental states all play important roles, particularly in the large group of men and women in whom there are no gross barriers to conception. This group with submarginal fertility comprises about 40 per cent of all the couples who are studied in large sterility clinics. These are the men and women who should and would have children if we knew more about the basic factors involved in fertility.

Age is a very important factor in both male and female fertility. Data presented by Barns, Campbell and Snaith[1] (table 1) show that women under 20 years of age conceived within three months whereas women 35 years and older required an interval of 42.4 months for conception to take place. Thus there is a rapid diminution in fertility in women after 35 years of age and this is accelerated beyond 40. Recent data on the male indicate that although the decline in his fertility curve is not as steep as in the female, nevertheless the pattern is similar. Thus no time should be lost in instituting a sterility study once the patient consults a physician.

TABLE 1

TIME INTERVAL FOR CONCEPTION IN NORMAL WOMEN ACCORDING TO AGE OF PATIENT*

AGE (YEARS)	TIME (MONTHS)
Under 20	2.9
21-24	7.3
25-29	15.0
30-34	27.1
Over 35	42.4

*From Barns, Campbell and Snaith.[1]

General health is important in fertility. A complete physical examination should be a part of every sterility study. Should the patient conceive, it is important that there be no contraindications to pregnancy. If the patient is obese, weight reduction is desirable. Exercise is in order for the sedentary individual. A good state of nutrition will result in increased fertility. Gross nutritional deficiencies are not common in this blessed land of ours but an increased protein intake is desirable. It is pertinent to recall that in serious nutritional deficiencies in women such as occurred during the war, menstruation ceased and fertility disappeared. Reproductive function was the first to be affected by serious malnutrition.

The Sterility Investigation

A complete medical history of both husband and wife is essential to the proper evaluation of the causes of infertility. In that the wife usually seeks medical advice, her history is likely to be the more detailed. It should include serious medical illnesses, major surgical procedures, a menstrual history, previous pregnancies and their complications, and sex practices. Detailed information concerning menstrual function is essential. Specific data concerning the length of time a pregnancy has been desired, the use of contraceptives, marital adjustment and previous examinations for sterility are noteworthy. The husband's history should include any facts which could influence spermatogenesis, such as the type of work he does, exercise, excessive use of alcohol or tobacco, and exposure to extreme heat or sources of radiation. If either partner has been married previously the history should include information concerning pregnancies and sexual experiences in former marriages.

Pelvic examination should be thorough. Note the development of secondary sex characters including the hair pattern. The urethra and Skene's and Bartholin's glands should be carefully palpated and discharges examined

microscopically. These areas may harbor residual infection. The cervix should be palpated and visualized, and abnormal cervical discharge examined for any pathogenic bacteria. The size, position and mobility of the uterus will provide pertinent information as to congenital abnormalities, neoplasms, retrodisplacements and pelvic inflammatory disease (figures 1 and 2). The adnexa should be freely movable and the ovaries may or may not be palpable. Adnexal tenderness, fixation or prolapse into the cul-de-sac may be significant. The environmental organs may contribute to pelvic pathology.

The usual laboratory examinations should be a part of the complete physical examination. The basal metabolism should be measured, for thyroid function is intimately associated with gonadal function. It is not necessary to demonstrate evidences of hypothyroidism, for moderate degrees of hypometabolism in the absence of physical findings may result in moderate degrees of ovarian failure.

Study of the male—It is desirable that a complete physical examination be carried out on the husband, including careful study of the reproductive organs. If gross abnormalities are uncovered he should be referred to a urologist. If his organs and sex pattern are normal a semen analysis should be carried out. It should be made under optimal conditions, when coitus has not been too frequent and preferably after a period of four to five days of abstinence. In addition to the actual count

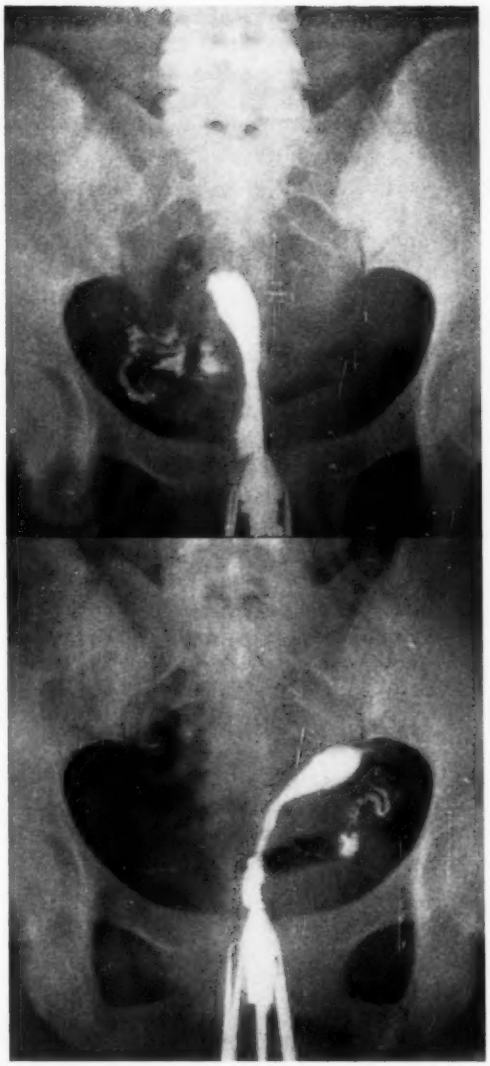


FIGURE 2. Both horns of the uterus and fallopian tubes in figure 1 are visualized separately.

FIGURE 1. A hysterosalpingogram of a patient who presented a complete lack of fusion of the müllerian ducts resulting in a double vagina and a double uterus.

and motility, sperm survival for 24 hours should be observed, and stained smears examined for sperm morphology. According to accepted standards, 3 to 5 cc. of semen should contain 60,000,000 sperm per cubic centimeter of good motility, with no more than 20 per cent abnormal forms, in order to qualify as a fertile specimen. However, exceptions are not uncommon. The same individual may show wide variation in sperm counts at different times and under different conditions. Should the original semen analysis prove substandard, further examinations should be made before deciding the status of the male partner. If the specimen obtained is considered fertile, the following procedures are then carried out.

Study of ovarian function—The normal fertile woman has regular ovarian cycles which are correlated with the menstrual function. At the end of the menstrual flow, follicles in the ovaries begin to grow under the influence of the follicle-stimulating hormone from the pituitary gland. These growing follicles produce estrogenic hormone which promotes the growth of the endometrium. About two weeks after the onset of the preceding period a widespread atresia of most of the growing follicles takes place and the dominant follicle, the one destined to ovulate, rapidly reaches complete maturity and ruptures to release the ripe ovum. The spurt in the growth of the follicle as well as ovulation are the result of the luteinizing hormone released by the pituitary gland. The collapsed follicle wall is now rapidly converted into the corpus luteum which not only continues to produce an increased amount of estrogenic hormone but in addition provides the pregnancy hormone, progesterone. The life of the corpus luteum is 13 or 14 days unless fertilization and implantation of the egg occur, when its continued endocrine function is maintained by chorionic hormone produced by the early gestation. Failure of conception and implantation results in rapid regression of the corpus luteum and a cessation of its endocrine activity. The sudden loss of hormonal support results in the onset of endometrial sloughing, regression and menses (figure 3).

These physiologic events occur rhythmically at varying intervals in different women.

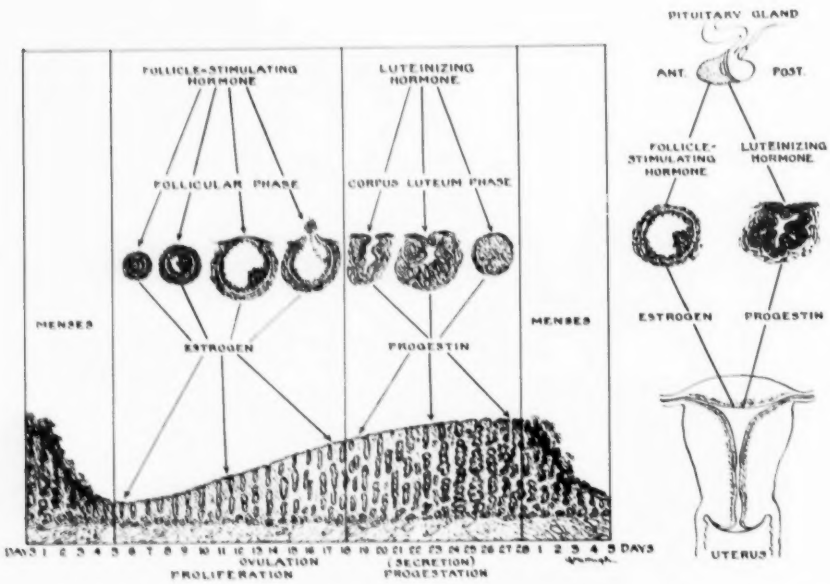


FIGURE 3. A diagrammatic presentation of the hormonal relationship of the pituitary, the ovaries and the endometrium in the normal menstrual cycle.

The pattern is rarely disturbed unless illness, some endocrine derangement or pregnancy ensues. Thus the woman who has regular menstrual periods probably ovulates with a fair degree of regularity. However, the woman who menstruates at grossly irregular intervals or has long or short periods of amenorrhea may exhibit anovulatory cycles. Siegler[2] in 1952 studied a group of 935 patients who desired to become pregnant and noted anovulatory periods in 5.77 per cent.

Gonadal function in the female can be evaluated in a variety of ways. An endometrial biopsy can be obtained at the onset of bleeding. The histologic section will reveal typical progestational changes if ovulation occurred and the corpus luteum was functional. The absence of progestational changes in the endometrium indicates an absence of ovulation. There is some evidence that histochemical studies of the endometrium will reveal deficiencies in hormonal function of the corpus luteum.

A second method of studying ovarian function is to measure the quantitative output of progesterone by the corpus luteum by determining the amount of urinary pregnanediol in the latter part of the cycle. Normally, this urinary metabolite of progesterone is either absent or present in small amounts, but in an ovulatory cycle 5 mg. or more is eliminated each day following ovulation. Daily vaginal smears will likewise indicate the presence of an ovulatory cycle.

The cervical mucus undergoes changes during the cycle as a result of the hormonal influences. As ovulation approaches it is clear and translucent, containing a high percentage of water, and it can be pulled out into long strands—spinnbarkeit. When this mucus dries, crystals of sodium chloride form providing a fernlike pattern. This phase in the cervical mucus provides for optimal sperm migration and probably facilitates fertilization.

The most practical method of studying the ovarian cycle is by the use of basal body temperature records. It has the advantage of simplicity whereas the other methods involve laborious laboratory procedures. Ovulation and corpus luteum formation are reflected in the normal daily temperature fluctuations. Thus the transition of the basal temperature from its low preovulatory to its elevated postovulatory level represents the ovulatory period. Although the exact time of ovulation cannot often be pinpointed on the graph, its occurrence can be confined within a 24 to 72 hour period. This transitional zone is the period of optimum fertility.

Continuation of an elevated temperature beyond the usual 13 or 14 days is due to the continued elaboration of progesterone by the corpus luteum, whose regression is prevented by chorionic gonadotropin produced by early pregnancy. Very early in the gestation, however, the chorionic cells take over the production of estrogens and progesterone. Although the amount of progesterone continues to increase as the pregnancy advances, the basal temperature tends to seek a lower level in the latter half of the pregnancy. There is no explanation for this (figure 4).

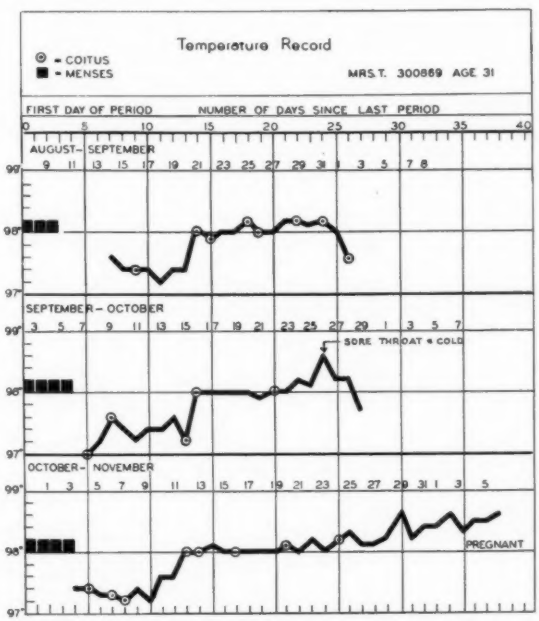


FIGURE 4. The basal body temperature graph of a normal fertile woman. Note that the transition of the curve from the low preovulatory level to the elevated postovulatory level occurred about day 12 or 13. This is the ovulatory and fertile phase of the cycle.

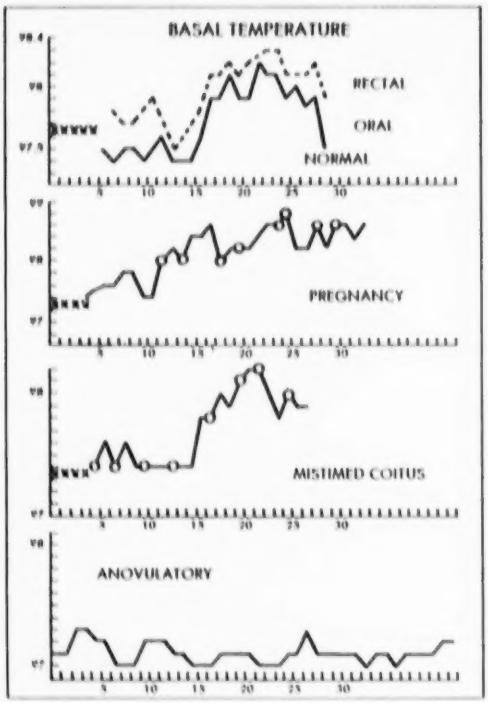


FIGURE 5. A series of basal body temperature graphs demonstrating important features.

Only a few simple instructions to the patient are necessary for preparing an informative basal temperature record. An oral thermometer with clear markings should be used so that the scale can be read easily. Any good thermometer will do, but the usual household fever thermometer is difficult to read, since the scale is long and the markings are close together. Basal thermometers are available with a short scale which can be read more easily. The scale extends from only 96 to 100° F., well within the range of healthy persons. Such a thermometer is a good investment for the patient.

The thermometer and a suitable record sheet should be kept at the bedside. As soon as the patient awakens each morning she places the thermometer in her mouth, obtains the reading and records it promptly on the graph by placing a dot in the proper square. If intercourse has taken place during the previous evening the dot on the record should be circled. After a woman has taken her basal temperatures regularly for several weeks, the process becomes a simple routine.

There is no advantage in recording rectal or vaginal temperatures. The former are no more accurate, although somewhat higher. It is much more simple to take oral readings (figure 5).

The graph will be more informative if the patient records her temperature at about the same time each morning. Irregular hours as well as physical and emotional disturbances are reflected in the temperature curve. The patient should be asked to record major variations in her normal pattern of living so that the physician can better interpret the graph.

One of the most common errors made by the woman who is keeping a temperature graph is the failure to understand that cycle days and the days of the month are not synonymous. She should be instructed to begin her temperature recording on the first morning of the menstrual period. This is cycle day 1. She continues to record basal temperatures throughout the month, but starts a new graph when the first day of her next period arrives. The temperature graphs of several months thus placed beneath one another allow an easy comparison of the cycles. The patient soon becomes familiar with the pattern of her menstrual cycles, and gross abnormalities will be easily discernible (Davis[3]).

Demonstrate that sperm and ovum can meet—A patent reproductive passageway is necessary for the sperm and ovum to meet in a fallopian tube where fertilization takes place. This patency can be demonstrated by the Rubin test which consists of the passage of carbon dioxide gas through the uterus and tubes and into the peritoneal cavity. This basic procedure in the study of sterility is usually carried out following a normal menstrual period. If endocervicitis is present it should be cleared up prior to this test. Recent clinical evidence of pelvic inflammatory disease is likewise a contraindication to the procedure.

The Rubin test can be carried out in the office or in the outpatient department of a hospital. There are a number of instruments de-

signed for the delivery of measured amounts of gas under controlled conditions and for the simultaneous kymographic recording of the pressure of gas flowing through the tubes. Normal tubal peristalsis can be demonstrated or the pattern of the waves may be indicative of partial obstruction. Such records provide valuable information concerning patency as well as tubal pathology. When there is a free passage of gas through the tube, rales can be heard by auscultation over the tubal areas. Gas will accumulate under the diaphragm where it will cause shoulder pain and it can be visualized fluoroscopically.

It is well to give the patient atropine, 1/150 gr., and phenobarbital, ½ gr., about an hour prior to examination. This will reduce the likelihood of tubal spasm. Pressures will reach 100 to 120 mm. mercury and drop somewhat in normally patent tubes. Rhythmic contractions are recorded on the kymograph. If an obstruction is present the pressure under which the gas is allowed to flow into the tube can be increased to 200 or even 250 mm. of mercury. The pressure may drop suddenly, indicating a sudden disappearance of the spasm or the release of filmy adhesions. Several attempts may be made to obtain the passage of gas, but if this fails, visualization of the uterus and fallopian tubes is indicated (figure 6).

Hysterosalpingography is the diagnostic procedure of choice in demonstrating the normalcy of the uterine cavity and the normalcy and patency of the fallopian tubes. Until very recently nonabsorbable radiopaque solutions were used and occasionally these fluids caused irritation and even damage to the tubes. However, in the past several years absorbable media have been introduced which provide good x-ray pictures. Sufficient data have not accumulated to demonstrate their lack of irritation to the pelvic structures. However, when it has been definitely confirmed that they are nonirritating, the use of fluid media will replace the use of gas. It is far better to watch the passage of a radiopaque substance through the uterus and fallopian tubes than to pass a gas unseen (figures 7 and 8).

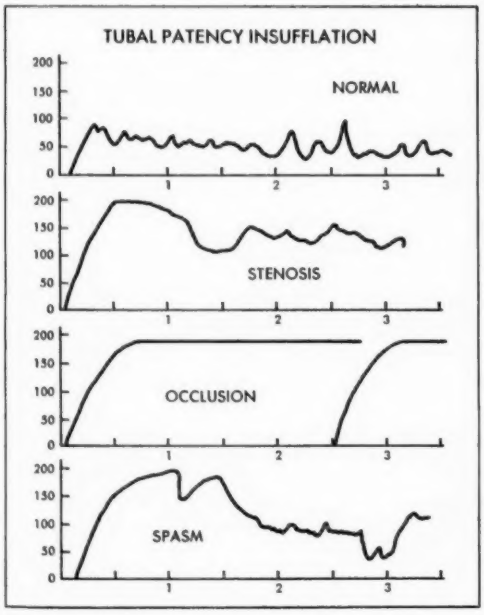


FIGURE 6. Kymographic tracings of normal and abnormal Rubin tubal insufflation procedures.

FIGURE 7. A hysterosalpingogram made with the use of an absorbable medium (SALPIX®) demonstrating a block in the left tube but a normal patent right tube. This patient conceived promptly following her sterility study.

FIGURE 8. Kymographic tracing showing tubal block induced by spasm of the fallopian tubes. Following the administration of an antispasmodic drug the uterine cavity and the left fallopian tube were visualized. This patient conceived soon after this study.

The fluid is passed under controlled pressure in the fluoroscopic room and its progress is followed on the screen. The uterus fills, and then the tubes, and when they are patent the flow continues into the peritoneal cavity. The rapid absorption of these substances makes it necessary to obtain several sets of films as the reproductive passageway is filling. If too long an interval elapses the pictures will have little value. Proper technic will provide excellent information concerning the uterus and tubes. This procedure can be repeated if the information obtained is questionable (figure 9).

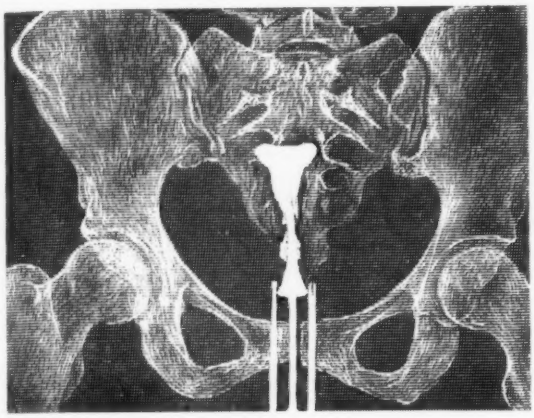
Stein has pioneered the use of pneumoperitoneum as an adjunct to hysterosalpingography. Carbon dioxide gas can be introduced into the peritoneal cavity through the fallopian tubes, if they are patent, or through the abdomen. X-ray films will visualize the pelvic organs. This approach is particularly useful in outlining large cystic ovaries as in Stein-Leventhal syndrome or abnormalities of the uterus.

The most recent diagnostic aid in the study of sterility is culdoscopy. A cystoscopelike instrument, the culdoscope, can be introduced through the posterior vaginal vault and the adnexa can be visualized directly. Endometriosis, tubal adhesions and other pathology can be diagnosed by inspection. These special diagnostic procedures are useful to the specialist but they are seldom necessary or desirable in the management of sterility by the general practitioner.

Therapy

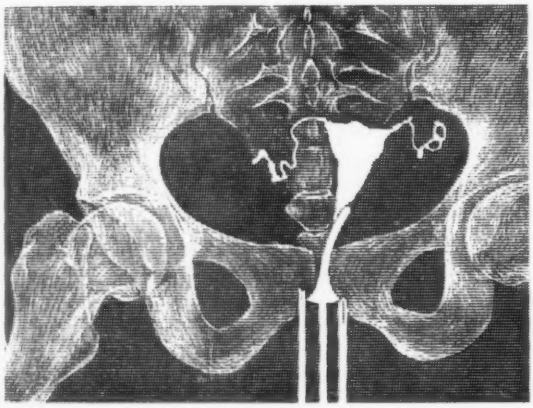
A complete sterility study is the most important therapeutic tool in the treatment of human infertility. It is impossible to assess the value of the various diagnostic procedures, but the demonstration of tubal patency by gas or radiopaque material is credited with the greatest importance. However, a careful study will uncover many factors which may decrease fertility such as ignorance of the reproductive process, an abnormal sexual pattern, or psychogenic factors. It has been estimated that at least one out of three couples who consult the family physician has children but no more than 25 per cent of couples who attend sterility clinics are successful. Specific therapy is still in its infancy. About 40 per cent of the last 500 couples studied at the Chicago Lying-in Hospital had no gross barrier to conception. These were fairly normal

FIGURE 9. Illustrations made from hysterosalpingograms demonstrating a variety of abnormalities visualized by an opaque oily medium.

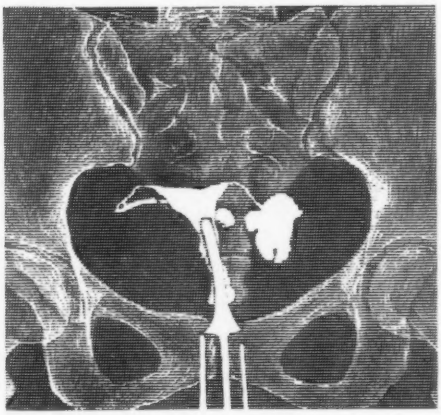


a. Neither tube is visualized indicating cornual block.

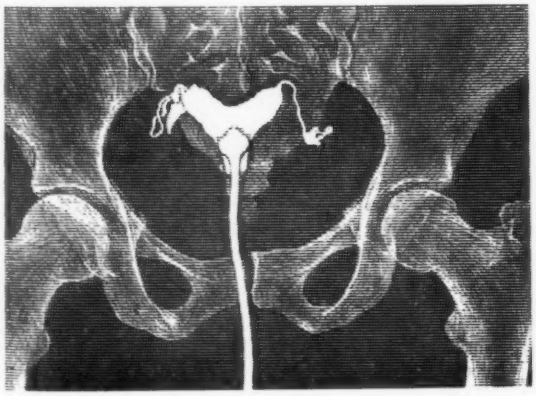
b. Only a small portion of one tube remains on one side. The opposite tube is greatly elongated, adherent and closed at the ostium.



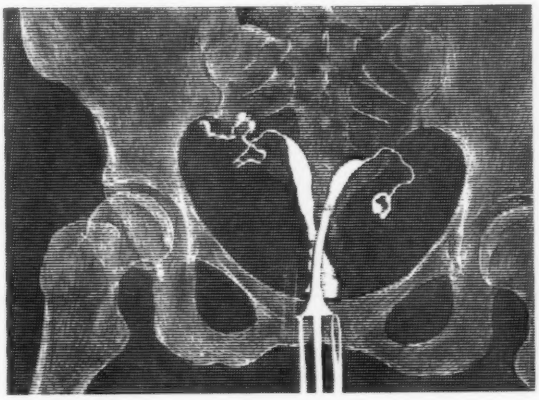
c. The uterus and fallopian tubes are visualized but no peritoneal spill could be seen.



d. Marked hydrosalpinx formation.



e. A bicornate uterus with normal patent fallopian tubes.



f. Complete uterine horns and normal fallopian tubes.

TABLE 2

ETIOLOGY OF INFERTILITY
(CHICAGO LYING-IN HOSPITAL; 500 COUPLES, 1950-1953)

ETIOLOGY	CASES	
	Number	*Per Cent*
Tubal factors		
1. Bilateral occlusion	85	17
2. Unilateral occlusion	104	20.8
3. Partial occlusion (Rubin)	12	2.4
Hormonal factors		
1. Irregular periods (sporadic ovulation)	41	8.2
2. Anovulatory cycles (severe gonadal failure)	9	1.8
Metabolic factors (hypometabolism)		
1. −10 to −20	123	24.6
2. Lower than −20	17	3.4
Male factors		
1. Azoospermia	4	0.8
2. Oligospermia	145	29
Pelvic tumors	29	5.8
Unknown factors (no demonstrable pathology)	197	39.4

women married to fairly normal men who failed to have children even though there were no obvious factors to account for their lack of fertility (table 2).

Prophylaxis—The developmental period in young boys and girls is an important period for intelligent medical supervision. The family physician should see that the establishment of the menses occurs at the proper time, that normal secondary sex characters develop and that the young girl is cognizant of healthy sex hygiene. A great delay in the onset of maturity should warrant medical study. The young girl may be overweight or sedentary in her habits or exhibit a hypometabolism. These may be corrected by wise counsel.

Grant[4] of Sydney, Australia, studied 133 patients who had ectopic pregnancies and subsequently failed to conceive. In 67 per cent the remaining tube was blocked. Thus the patient who develops an ectopic early in her reproductive lifetime should be subjected to patency studies of the remaining tube soon after surgery with the hope that its patency may be maintained.

Gonadal failure—Irregular menses or long periods of amenorrhea are often associated with sporadic ovulation or its complete absence. It was the most important factor in 5.77 per cent of 935 cases of sterility studied by Siegler. In our most recent 500 patients irregular menses and only sporadic ovulation were present in 8.2 per cent, and severe gonadal failure in 1.8 per cent.

Abnormal ovarian function is usually secondary, having its origin in the pituitary gland, other endocrine glands or systemic disorders. In mild or moderate degrees of hypoovaria, clinical findings may be entirely absent. More severe degrees which existed prior to puberty will be manifested in a lack of normal development of skeletal and secondary sex characters and infantile pelvic organs. If the failure developed later in life a regression or even atrophy of the pelvic organs and secondary characters will occur as a result of estrogen deficiency.

It may be associated with the so-called Stein-Leventhal syndrome in which the ovaries become large, oyster-pearl in appearance and cystic. Such polycystic ovaries probably develop as a result of an abnormal pituitary or other glandular stimulation and the condition is rarely reversible. When a diagnosis of this condition is made, wedge resection of liberal portions of each ovary results in a return of menses, ovulation and pregnancy in 75 per cent of cases. This unphysiologic approach to the therapy of this condition may so disturb the abnormal endocrine balance that normal function is resumed (Stein[5]).

Gonadal suppression may result from adrenal overactivity. These patients exhibit an increase in ketosteroid production in addition to amenorrhea and an absence of ovulation. They respond to cortisone therapy.

The young woman with irregular menstrual periods or long periods of amenorrhea should be studied by the physician to determine how often ovulation does occur. Basal temperature curves and endometrial biopsies at the onset of bleeding will provide information concerning the gravity of the ovarian failure. If sporadic ovulations do occur, it can be considered moderate in degree. Long periods of amenorrhea and a complete absence of ovula-

tion indicate severe degrees of failure. If the patient is overweight, an intelligent reduction may have a wholesome influence on ovarian function. Thyroid extract can be administered to the individual with hypometabolism. A crude rule for dosage is to administer about 1 gr. of thyroid extract for every −10 of the basal rate up to a maximum of 3 gr. daily. Obviously most of the patients encountered do not have hypothyroidism but many will develop improved ovarian function on the thyroid medication. If the patient does not respond to these simple measures or has severe ovarian failure it is wise for the physician to refer her to a specialist or an endocrine clinic where she can be studied thoroughly and treatment recommended (Davis[6]).

The various hormonal preparations such as estrogens, progesterone, and chorionic and anterior pituitary lobe preparations are of little value in the therapy of gonadal failure. Theoretically, a potent gonadotropic extract from the anterior lobe which would contain follicle-stimulating and follicle-luteinizing fractions would prove extremely useful in ovarian failure. Such a substance is not available today but present interest in pituitary hormones may result in its early discovery (Davis[7]).

Irradiation therapy of the ovaries and the pituitary gland has been used for many years. The enthusiasts have reported fairly good results in selected patients. However, most workers in the field of sterility have not been convinced that this method is sufficiently useful to ignore its potential dangers.

Tubal reconstruction—The tubal factor is the most important cause of infertility in the female. The oviducts may be blocked resulting in absolute sterility. The lumina may be partially blocked by internal adhesions of tubal folds or external environmental adhesions resulting from an old pelvic inflammatory disease. Gas and fluid may be forced through the tube under high pressures but the pathologic changes decrease the likelihood of an egg and sperm meeting. Such oviducts increase the incidence of ectopic gestation greatly. The gross thickening of the tubal wall and external adhesions decrease tubal peristalsis, an important factor in egg transport. Lastly, only one tube may be patent or the opposite tube may have been removed. Unfortunately, the frequency of unwarranted pelvic surgery often results in the removal of an ovary so that the patent tube has no adjacent ovary. We have demonstrated that migration of the egg from an ovary to the opposite tube is a rare or an almost impossible occurrence.

Of the last 500 cases of infertility we studied, bilateral tubal occlusion was present in 17 per cent, unilateral occlusion in 20.8 per cent and partial occlusion in 2.4 per cent (table 2). Thus, in half of the women who were examined in our sterility clinic, the tubal factor was an important consideration in their sterility. This incidence is higher than seen by the general practitioner, for the majority of the patients in our clinic have been under the care of one or several physicians because of their failure to conceive.

The treatment of partial tubal block is best carried out by repeated attempts at forcing carbon dioxide gas through the lumina at controlled pressures. Usually it is safe to use a maximum of 250 mm. mercury and the pressure should be dropped if this provokes pain. Periodically, the uterus and tubes can be visualized by the use of an absorbable medium to note whether progress has been made. If there is no evidence of improvement, laparotomy and surgical relief of adhesions may be considered by the specialist.

Tubal plastic operations for the relief of sterility are carried out on selected patients in sterility clinics. The most favorable cases are those in which a minimum of surgery is necessary to restore patency. This occurs most often where environmental adhesions are responsible for the tubal closure. Closures at the ostium are more often amenable to surgical reconstruction than blocks in other areas. New surgical technics such as the use of polyethylene tubes to maintain patency and to facilitate the reimplantation of a severed tube into the uterine cavity, and plastic films to hood the tube during healing have increased the number of tubes which remain patent. However, patency to gas or fluid is not synonymous with a return to normalcy. Many of these oviducts have been so damaged by the

inflammatory process that they do not provide for normal reproductive physiology and patients do not get pregnant. Newer methods have not increased the pregnancy rate much above 10 or 20 per cent in most clinics. However, even these results justify the surgical procedures in selected cases.

Surgery on pelvic organs—Undoubtedly there are instances in which abnormal positions of the uterus, such as extreme retrodisplacements, decrease fertility. Rarely, however, are any surgical attempts at correction justifiable. Large groups of patients who were subjected to such operations in the past did not show increased fertility.

Curettage is still a common therapeutic measure in the management of infertility in women. It has no value other than that it provides endometrium for histologic study.

Myomas are found much more frequently in women who are infertile than in normal women. The incidence in our recent study was over 5 per cent. Myomas are usually the result of the sterility and rarely its cause. Myomectomy is occasionally practiced but the removal of some of the tumors rarely improves fertility. Often such myomectomies are the prelude to a hysterectomy later.

Endometriosis definitely decreases fertility. How this occurs is not known, for the endometrial implants and small cystic masses rarely cause tubal occlusion. If patients with early endometriosis fail to conceive after a complete investigation during which other major factors have been ruled out, surgery is advisable. At operation as much of the endometriosis as possible should be resected without impairing subsequent fertility. The process can be inactivated for a time by the administration of moderate doses of diethylstilbestrol but this is accomplished by suppressing ovarian function. The drug can be stopped and menses will recur.

Psychotherapy—In our most recent study 39 per cent of the couples were regarded as normal for no major pathology which would have a bearing on their fertility could be demonstrated. Obviously many intangible factors enter into the fertility of an individual. Emotional factors may play an important role. Psychotherapy is indicated and it is here that the family physician who knows husband and wife intimately and who has earned their confidence may play an important role. He may wish the help of the specialist in evaluating major psychiatric problems but his wise counsel will suffice in most instances.

When the diagnostic survey has been completed, an informal discussion with the couple should be arranged. The results of the various procedures should be explained to the husband and wife and their significance pointed out. The instructions should include everything which may increase fertility. The fertile period should be emphasized and the sex pattern changed so that coitus will occur most often during this period. Douches should be avoided. Exercise, diet and weight reduction, where necessary, are important. Intelligent periodic follow-ups may elicit important information and represent good psychotherapy.

It is of interest that 61.7 per cent of patients who conceived in the group presented here became pregnant within six months following the sterility study (table 3). In Bender's[8] study 46.3 per cent became pregnant, of which 50 per cent conceived within six months and 66 per cent within a year. Medical supervision should continue during the early months of pregnancy for abortion is almost twice as common in women studied for infertility as in fertile women and the incidence of ectopic gestation is three or four times as great. It is a sterile experience to become pregnant and to have no baby.

TABLE 3

TIME INTERVAL FROM STERILITY STUDY TO CONCEPTION (CHICAGO LYING-IN HOSPITAL; 500 COUPLES, 1950-1953)

DURATION	PERCENTAGE	
0-1 month	25.3	
1-2 months	11.1	
2-3 months	9.5	61.7
3-4 months	9.5	
4-5 months	6.3	
5-6 months	—	
6-12 months	23.8	
1-2 years	12.6	
2-3 years	1.5	
Over 3 years	—	

When it has been demonstrated that either the husband or the wife is incapable of reproduction the family should be apprised of this condition. Unless the sterility is absolute it is better to give a guarded prognosis, for pregnancies do occur when least expected. If the husband has a severe oligospermia with an occasional sperm present in the seminal fluid the couple should be informed that although the husband is not sterile nevertheless a pregnancy is most impossible.

When the husband has an azoospermia or a severe oligospermia, artificial insemination using donor sperm can be suggested if religious beliefs condone such practices. However, a decision to resort to such a procedure must be left to the husband and wife. It is wise to refer these patients to specialists who have had considerable experience with this procedure. It should not be undertaken by the family doctor for too many extraneous problems may arise.

Adoption should be suggested to the couples who cannot have children. It is important that the decision to adopt a child not be delayed too long, for the various placement agencies will not consider foster parents who have reached middle life (husband or wife over 40 years old). Furthermore it may take from one to three years to obtain a baby after the application has been approved. The physician can help the family to obtain a baby by referral to proper agencies and by his recommendation of the patients. The sterility study has been completed only when the couple has a baby as a reward for its efforts.

Summary

A complete sterility study should be carried out in every couple who consult a physician because of their inability to have children. A carefully conducted diagnostic survey is the best therapeutic regimen for infertility. Such a study can be carried out by the family doctor, and rarely he may need help from the specialist in this field.

REFERENCES

1. Barns, Tom, Campbell, H. and Snaith, L.: Failure of therapy in management of infertility. J. Obst. & Gynaec. Brit. Emp. 60:670-679, 1953.
2. Siegler, S. L.: Treatment of sterility resulting from anovulatory menstruation. Fertil. & Steril. 3:480-499, 1952.
3. Davis, M. E.: Natural Child Spacing. New York, Garden City, 1953.
4. Grant, Alan: Problems in fertility and sterility due to ectopic pregnancy: A study of 259 cases. M. J. Australia 2:817-819 (November 28) 1953.
5. Stein, I. F.: Management of bilateral polycystic ovaries. Fertil. & Steril. 6:189-205 (May-June) 1955.
6. Davis, M. E.: Recent trends in the study of infertility. Ann. New York Acad. Sc. 54:845-863 (May) 1952.
7. ———: Primary ovarian failure. J. Clin. Endocrinol. 13:1551-1554 (December) 1953.
8. Bender, S.: End-results in primary sterility. Brit. M. J. 2:409-413 (August 23) 1952.

MEETINGS *and Postgraduate Courses*

University of Texas, Houston: Practical bedside cardiology, March 14-17, under the direction of Dr. Samuel A. Levine, Clinical Professor of Medicine, Harvard Medical School. Further information may be obtained from the University of Texas Postgraduate School of Medicine, Texas Medical Center, Houston 25.

University of Minnesota, Minneapolis: Continuation course in pediatrics for general physicians, March 5-7, at the Center for Continuation Study, under the direction of Dr. John A. Anderson, Professor and Head, Department of Pediatrics. Guest faculty will include Dr. Katherine Dodd, Professor of Pediatrics, University of Arkansas School of Medicine, who will also deliver the annual Phi Delta Epsilon lecture on March 6.

University of Minnesota, Minneapolis: Continuation course in cardiovascular disease for general physicians, March 19-21, at the Center for Continuation Study, directed by Dr. C. J. Watson, Professor and Head, Department of Medicine.

University of Minnesota, Minneapolis: Continuation course in dietetics for dietitians at the Center for Continuation Study, March 1-3, under the direction of Miss Angeline D. Mannick, Director of Nutrition and Associate Professor of Dietetics.

The Management of Acne Vulgaris in the 12 to 17 Year Age Group

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ACCORDING to current opinion, roentgen therapy is the most effective single modality for the treatment of acne vulgaris. It is also believed that roentgen rays should not be used routinely in patients under 17 years of age. As this paper discusses management of the disease in patients less than 17 years old, roentgen therapy will not be included.

A knowledge of the pathogenesis of acne appears pertinent as a logical basis for therapy. Acne vulgaris is, according to modern concepts, due to circulating, androgenic hormones that act on the "shock organ," the pilosebaceous apparatus (hair follicles and sebaceous glands). Although this is probably the essential factor in acne, there are doubtless other important contributing causes, such as formation of comedones, intrafollicular irritation from certain foods and drugs, foci of infection, insufficient secretion of thyroid hormone, iron deficiency anemia, application of skin creams, seborrheic dermatitis of the scalp and, probably, nervous stress. It is therefore essential to treat every facet, however minor, which may have a place in the etiology. With our present knowledge, the therapy for acne must be multiphasic.

One important consideration is the proper care of the pilosebaceous orifices. It is essential to prevent formation of comedones, or blackheads, at the opening of the pilosebaceous glands. When comedones are not removed, they will plug the pores' natural secretions and cause the development of papules, pustules and even cystic lesions.

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Since Straumfjord's[1] report concerning the benefits derived from vitamin A in cases of acne vulgaris, numerous publications on this therapy have appeared.[2-6] Lozza[7] reported the beneficial effect of vitamin C in the acne therapy, and, more recently, Morris[8] advocated its use in this condition.

In view of these favorable reports, we have attempted to evaluate the beneficial results derived from the administration of vitamins C and A. Patients with acne vulgaris were divided into three groups. Those in the first group were given 100,000 units of aqueous vitamin A daily; the second group, 1 gm. of ascorbic acid plus one 8 oz. glass of orange juice daily, and the third group, 1 gm. of vitamin C, orange juice and 100,000 units of vitamin A each day. All patients were instructed to avoid chocolate, nuts, peanut butter and fried foods, and each was given a lotio alba preparation for topical application. Before the therapy was started the patients were classified as 1+ to 4+, according to the severity of the acne condition; 1+ indicated mild acne and 4+ severe acne. We attempted to place an equal number of the severe cases (4+) in each of the three treatment categories.

Results

Group 1 (vitamin A therapy)—Of the 59 original patients in this group, 41 continued with the procedure and returned for adequate treatment and follow-up. Of this number, 26 (63 per cent) improved while 15 did not respond to the therapy.

Group 2 (vitamin C, 1 gm., and 8 oz. of orange juice daily)—Of 78 patients in this group, 64 returned for adequate treatment and follow-up. Of this number, 34 (53 per cent) improved; 30 failed to improve.

Group 3 (vitamin C, orange juice and vitamin A)—Of 63 patients in this group, 50 returned for adequate treatment and follow-up. Of this number, 44 (88 per cent) improved; only six did not respond to the therapy.

Comment

According to Sulzberger and Baer,[9] vitamin A appears to be important in keratinizing (and in lubricating) the skin's surface. In a later publication, Sulzberger and Wolf[10] stated that vitamin deficiencies, including vitamin C deficiency, are known to produce follicular hyperkeratosis, usually observed in adolescent acne vulgaris. Sure and associates[11] demonstrated that a depletion of vitamin A in the rat is followed by a fall in the concentration of ascorbic acid in the tissues. Mayer and Krehl[12] stated that one of the first symptoms of vitamin A deficiency is depletion of the animal ascorbic acid reserve, and that scorbutic symptoms may be cured with ascorbic acid. They also stated that ascorbic acid will prevent the appearance of vitamin A deficiency symptoms.

Hyperkeratotic papules in scurvy were first described in 1919 by Wiltshire, as reported by Goldsmith and Hellier.[13] Further investigation of hyperkeratotic papules was conducted by the British Medical Research Council with an experiment on diets deficient in vitamin C. One patient developed hyperkeratotic papules on the outer aspect of the upper arms after 17 weeks. This exacerbation occurred in all 10 volunteers after 26 weeks. Initially a few follicles were plugged by a horny material in which the hair was coiled or looped. These enlarged follicles became red a few weeks later. Pronounced exacerbation of previously mild acne was noted in 5 of the 10 cases.[14]

In our series it was found that many adolescents had diets low in calorie intake and particularly low in vitamins C and A. A dietary deficiency of vitamin C, demonstrated by low blood plasma levels, was present in approximately 18 per cent of these patients; the deficiency was due to poor eating habits.

Iron deficiency anemia was present in some girls. The addition of ascorbic acid to iron is advisable since experiments have shown that the absorption of food (tagged with radio-iron) increases with the simultaneous oral administration of either ascorbic acid or foods containing ascorbic acid.[15] Vitamin C is necessary to reduce dietary iron from the ferric to the more readily absorbable ferrous state.

Summary

We do not propose to imply that acne vul-

garis is a condition based primarily on the lack of vitamins C and A. However, our studies have shown conclusively that these vitamins are useful agents in correcting the follicular plugging present in acne vulgaris. Vitamin C is also beneficial in correcting iron deficiency anemia, a condition frequently present in adolescent patients. Orange juice is a good and pleasant source of vitamin C, and its intake should be encouraged in persons with acne vulgaris. Vitamins C and A proved to be more beneficial to acne patients when given simultaneously instead of separately.

REFERENCES

1. Strachwitz, J. V.: Vitamin A: Its effect on acne; study of 100 patients, Northwest Med. 42:219 (August) 1943.
2. Lynch, F. W. and Cook, C. D.: Acne vulgaris treated with vitamin A, Arch. Dermat. & Syph. 55:355 (March) 1947.
3. Davidson, D. M. and Sobel, A. E.: Aqueous vitamin A in acne vulgaris, J. Invest. Dermat. 12:221 (April) 1949.
4. Combes, F. C., Saperstein, R. B. and Distelheim, L.: Vitamin A in acne vulgaris, M. Times 77:473 (October) 1949.
5. Frazier, C. N. and Hu, C. K.: Nature and distribution according to age of cutaneous manifestations of vitamin A deficiency: A study of 207 cases, Arch. Dermat. & Syph. 33:825 (May) 1936.
6. Savitt, L. F. and Obermayer, M. E.: Treatment of acne vulgaris and senile keratoses with vitamin A: Results of clinical experiment, J. Invest. Dermat. 14:283 (April) 1950.
7. Lozza, M.: La vitamina C associata al calcio nella cura dell' acne juvenilis, Minerva med. 2:235 (September 8) 1939.
8. Morris, G. E.: Use of vitamin C in acne vulgaris, Arch. Dermat. & Syph. 70:563 (September) 1954.
9. Sulzberger, M. B. and Baer, R. L.: Acne vulgaris and its management, In: 1949 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1950, p. 13.
10. Sulzberger, M. B. and Wolf, J.: Dermatology, Essentials of Diagnosis and Treatment, Chicago, The Year Book Publishers, Inc., 1952, p. 263.
11. Sure, B., Tufts, R. M. and Harrelson, R. T.: Vitamin interrelationships, J. Biol. Chem. 129:215, 1939.
12. Mayer, J. and Krehl, W. A.: Relation of diet composition and vitamin C to vitamin A deficiency, J. Nutrition 35:523, 1948.
13. Goldsmith, W. N. and Hellier, F. F.: Recent Advances in Dermatology, Ed. 2, New York, The Blakiston Company, Inc., 1954, p. 213.
14. British Medical Research Council Accessory Food Factors Committee, Vitamin C Subcommittee: Vitamin C requirement of human adults; experimental study of vitamin C deprivation in man (preliminary report), Lancet 1:853 (June 5) 1948.
15. Moore, C. V. and Dubach, R.: Observations on absorption of iron from foods tagged with radioiron, Tr. A. Am. Physicians 64:245, 1951.

Postgraduate Clinical NOTES

45. TREATMENT OF BREATH-HOLDING ATTACKS

Treatment is not easy. It can be stated categorically that drugs are useless. In the early stage of an attack, before consciousness is lost, a sound slap on the face or buttocks, or the splashing of cold water over his face or head, may be enough to cause the child to inspire—and the attack stops immediately one breath is taken. If the next stages cannot be averted, the essential thing is to avoid a fuss, to pay as little attention to the child as possible when he recovers, and on no account to let him have his own way as a result of the attack. If he is standing at the beginning of an attack, he must be laid down; otherwise there is nothing to do but wait for the end of the fit. Unless the attack originated from pain or fear, the underlying causes must be sought—the underlying insecurity, excessive discipline or lack of discipline, and the reason for the child's need to adopt attention-seeking devices.

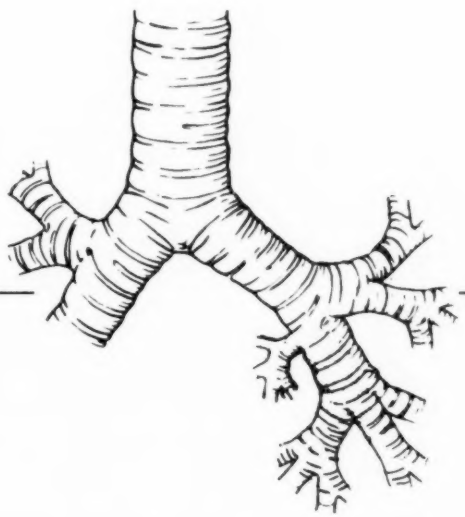
British Medical Journal, August 1955, pp. 422-23

SCIENTIFIC EXHIBIT

Bronchogenic Carcinoma

ROBERT R. SHAW AND DONALD L. PAULSON

University of Texas, Southwestern Medical School, Dallas



This exhibit was adapted for publication from a presentation prepared for display under the supervision of Dr. Louis Waters, Professor of Medical Art, Southwestern Medical School of the University of Texas.

THE SILENT PHASE

All bronchogenic carcinomas pass through a silent phase during which they can be diagnosed only by routine roentgenographic examination of the chest.

THE EARLY PHASE

Early symptoms of bronchogenic carcinoma are caused by the neoplasm breaking through bronchial mucosa, producing:

- Cough
- Localized wheeze
- Blood spitting
- Obstructive pneumonitis

THE LATE PHASE

- Cough
- Hemoptysis
- Pain
- Dyspnea
- Recurrent pneumonitis
- Hoarseness
- Weight loss

An abnormal shadow of unproved etiology in a chest x-ray, like a lump in the breast, may be carcinoma.

- A negative bronchoscopic examination does not rule out carcinoma.
- Exploratory thoracotomy is mandatory.

There is no characteristic symptomatic or roentgenographic pattern for bronchogenic carcinoma. Its early detection depends on a high index of suspicion.

DIAGNOSTIC PROCEDURES

History and physical examination

Roentgenograms

Bronchoscopy

Cytologic study of secretions

Study of pleural fluid for carcinoma cells

Biopsy of lymph nodes

Exploratory thoracotomy

Operative Mortality for Bronchogenic Carcinoma (1945-1954)*

Type of Resection	Number of Cases	Deaths	
		Number	*Per Cent*
Pneumonectomy	170	13	7.7
Lobectomy	116	4	3.4
Total	286	17	5.9

*Total cases 830; resectability rate 34.3 per cent.

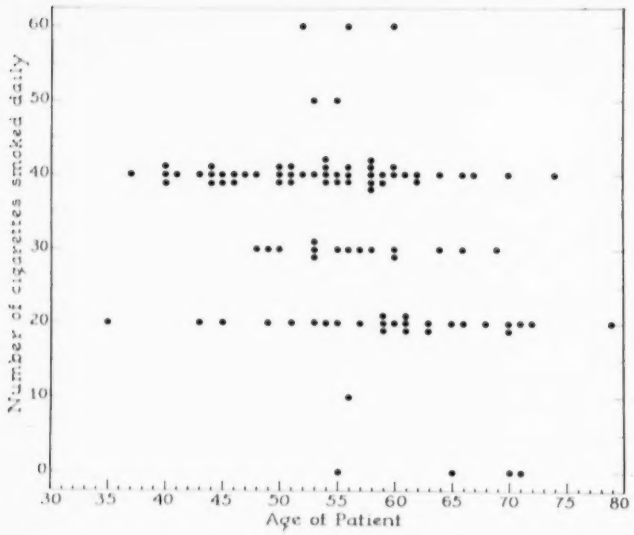
Surgical Survival Rates for Bronchogenic Carcinoma (Five Years or More) (1945-1950)*

Type of Resection	Number of Cases	Survivors	
		Number	*Per Cent*
Pneumonectomy	86	11	13
Lobectomy	40	8	20
Total	126	19	15

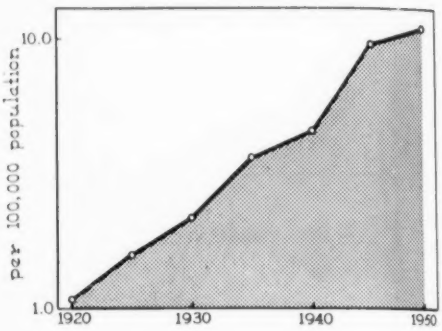
*Total cases 377; total number of patients surviving five years 25 (7 per cent).

Surgical Survival Rates for Bronchogenic Carcinoma (three years) (1951-1952)

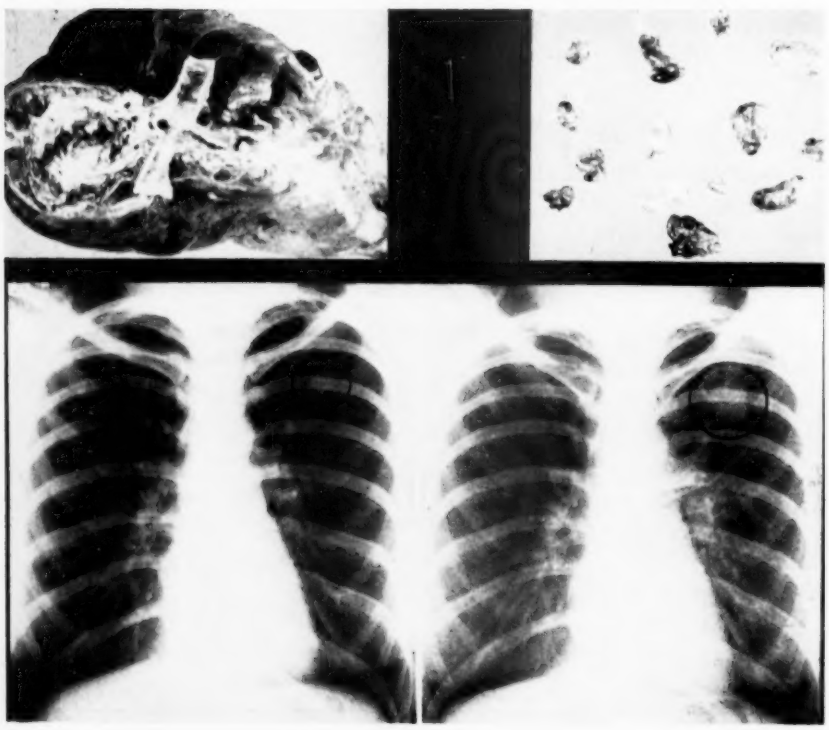
Type of Resection	Number of Cases	Survivors	
		Number	*Per Cent*
Pneumonectomy	39	8	21
Lobectomy	28	10	36
Total	67	18	27



Smoking history in 100 consecutive cases of bronchogenic carcinoma.

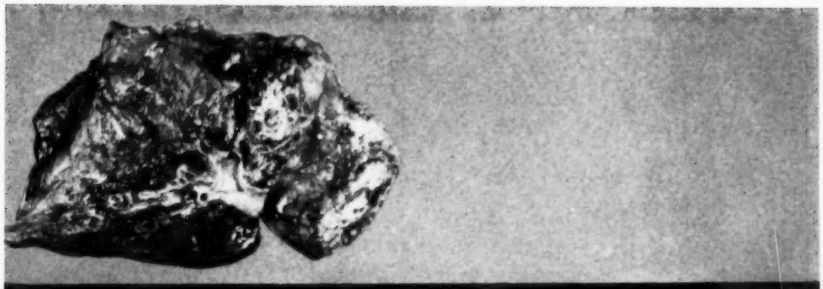


Deaths from bronchogenic carcinoma, which is now the most frequent visceral carcinoma in males and is increasing in incidence.

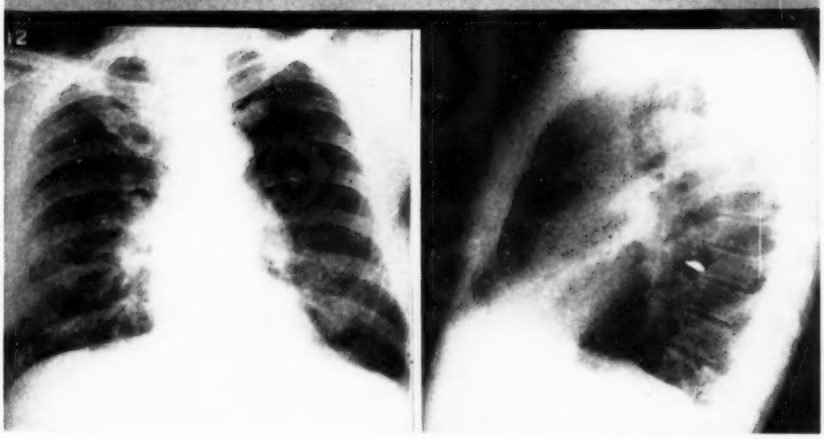


Silent adenocarcinoma in left lung of 36 year old woman. Specimen reveals carcinoma in upper lobe and involvement of 15 mediastinal lymph nodes.

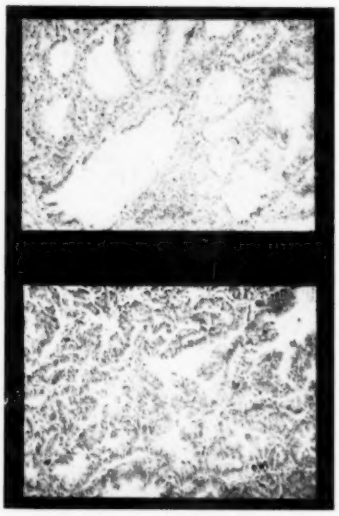
X-rays of chest reveal the presence of the lesion for 10 months. Roentgenogram on the left was made April 21, 1952, on a routine survey. That on the right was made February 5, 1953.



This neoplasm, almost entirely intrabronchial, had caused obstructive emphysema of entire left lung by partially blocking the main bronchus.

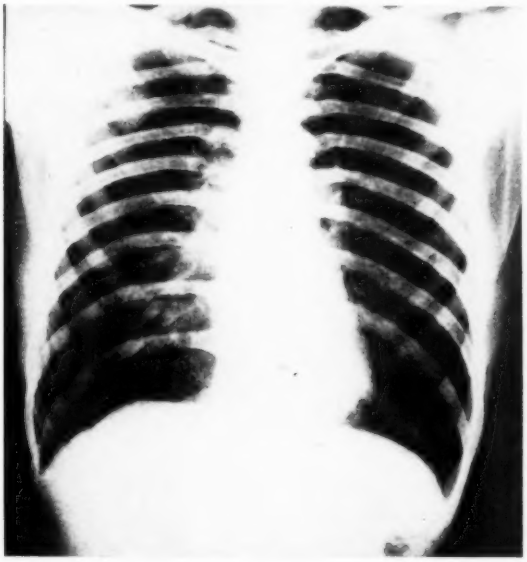


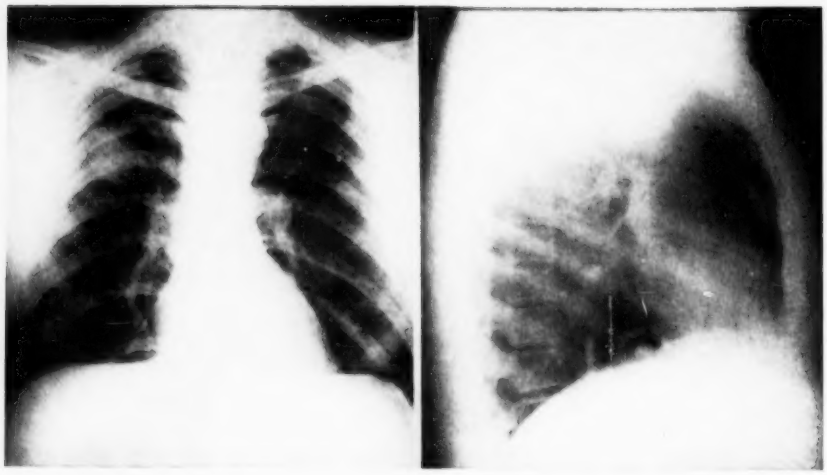
X-ray study of this 72 year old man does not show a shadow characteristic of a tumor, but emphysema of the left lung is evident. The patient complained of localized wheeze and shortness of breath. Bronchoscopy revealed neoplasm obstructing the left main bronchus.



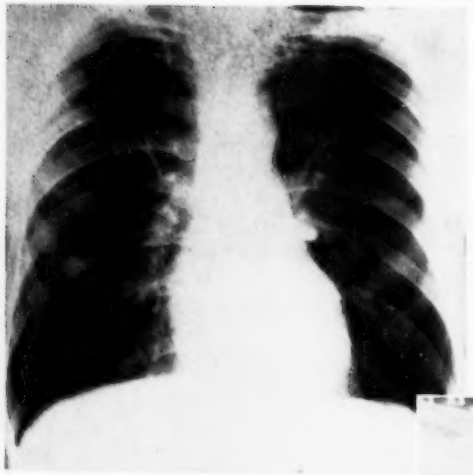
Photomicrographs show typical pattern of this tumor. The patient, a 43 year old man is alive and well three and one-half years after lobectomy.

Small alveolar cell carcinoma discovered during silent phase on a routine x-ray examination.

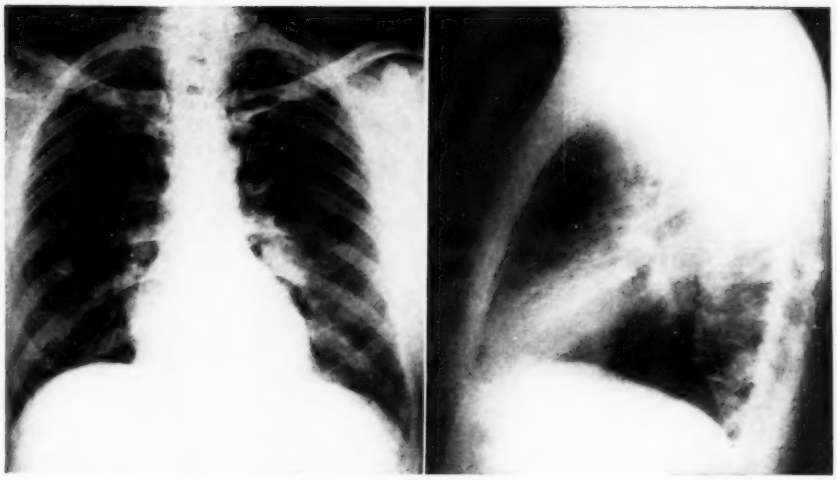




Asymptomatic round lesion of the right upper lobe. Bronchoscopic examination was negative. Exploratory thoracotomy revealed carcinoma. Right upper lobectomy was done.

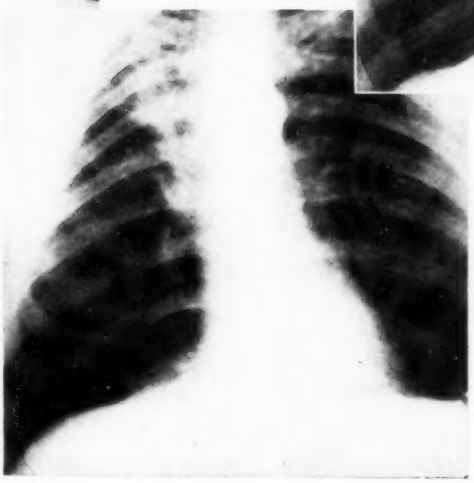


Small, undifferentiated carcinoma in the left lower lobe bronchus treated by lobectomy with excision of a portion of the main bronchus. The left upper lobe bronchus was sutured to stump of the main bronchus. The only sign of disease had been a pneumonitis which cleared with penicillin therapy. A bronchogram showed localized narrowing of lower lobe bronchus. Patient is alive and well two and one-half years later.



Asymptomatic lesion of the left lower lobe found on routine examination. Results of bronchoscopy were negative. Exploratory thoracotomy revealed epidermoid carcinoma of the left lower lobe, and lobectomy was done. The patient is alive and well more than four years later.

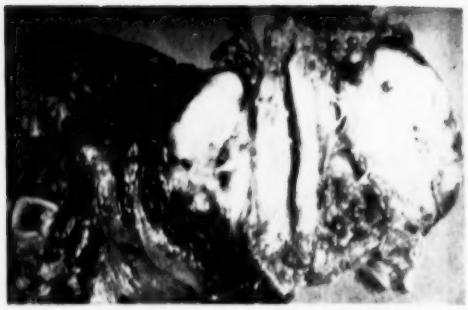
◀ Chest x-ray of 62 year old man taken in January 1948. The patient complained of cough, low grade fever and lassitude. Penicillin therapy for 14 days produced almost complete symptom relief.



An x-ray taken in June 1948 shows almost complete disappearance of shadow in right upper lobe. The patient was symptom-free at this time.

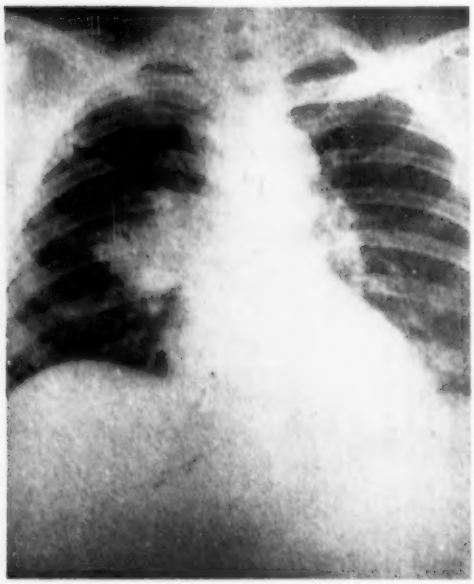
By December 1948, symptoms had recurred and a chest x-ray shows reappearance of the shadow in the same segment of the right upper lobe. Because pneumonitis had reappeared, bronchogenic carcinoma was suspected and thoracotomy advised. At surgery, a small neoplasm in a branch bronchus of the right upper lobe was found, necessitating total pneumonectomy.

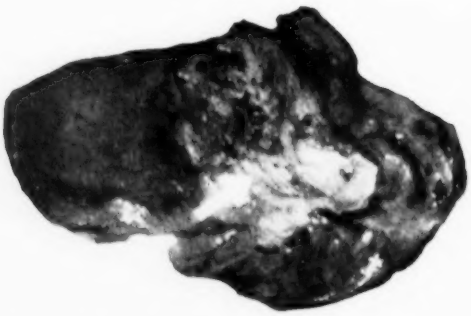
This squamous cell carcinoma caused pain radiating along the third right intercostal space. Patient was a 45 year old man. Note the destruction of the cortex of the third right rib posteriorly.



Resected specimen shows neoplasm invading third intercostal nerve.

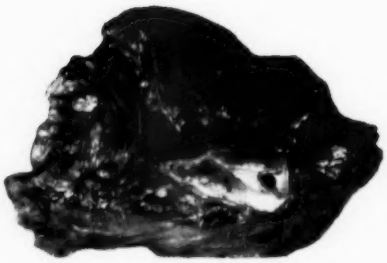
Detailed insert to show third intercostal nerve.





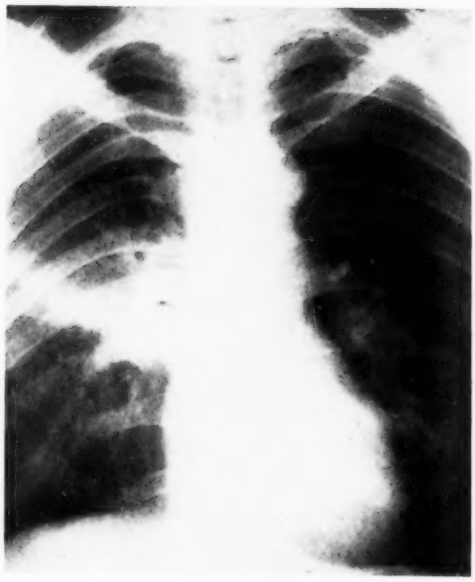
Abscess of lung beyond a small squamous cell carcinoma obstructing the dorsal bronchus of right lower lobe.

This 55 year old man experienced high fever initiated by a chill, cough, expectoration of foul pus, and localized pain in the right posterior chest. Bronchoscopy revealed a neoplasm in the orifice of the dorsal bronchus on the right. Dense shadow is caused by abscess beyond the small obstructing neoplasm.



Specimen reveals epidermoid carcinoma of the right lower lobe and main bronchus. Lymph nodes were not involved.

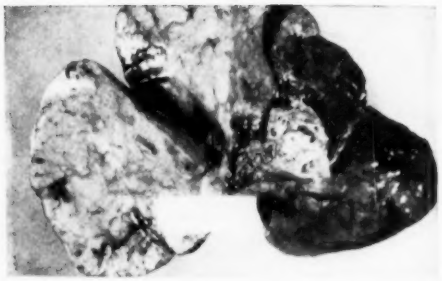
Patient complained of cough, wheeze and blood streaking of two months' duration. Pneumonia involving the right lower lobe improved with AUREOMYCIN® treatment. Fever recurred, and x-ray shadow persisted. X-ray of chest shown on right reveals chronic obstructive pneumonitis of right lower lobe. Results of bronchoscopic examination were positive for epidermoid carcinoma. On April 21, 1949, right pneumonectomy was done. The patient was alive and well nearly four years later.

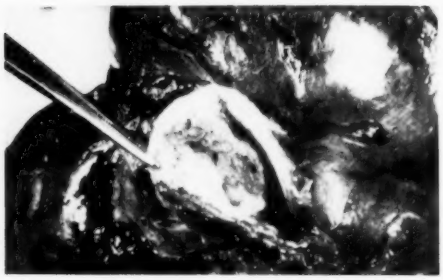


Severe pain radiating along the fifth intercostal nerve on the right was the only symptom produced by this small neoplasm which had invaded the fifth intercostal muscle bundle and bodies of vertebrae.

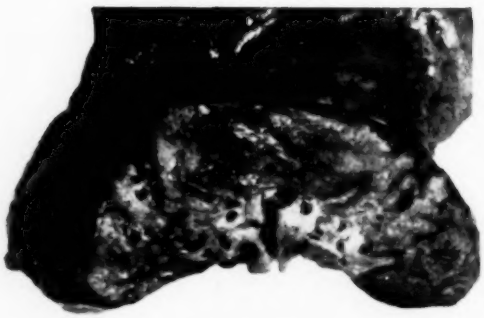
X-ray of chest taken 17 months after resection of small segment of the right upper lobe along with segments of the fourth and fifth ribs, intervening intercostal muscle bundles and portions of bodies of two vertebrae.

In 1945, three years before admission to the hospital, this 34 year old man experienced coughing and wheezing. In 1947, six months before surgery, he had hemoptysis, fever, brassy cough and dyspnea, and began to lose weight. X-rays disclosed obstructive pneumonitis of the right lower lobe and emphysema of the right lung. Bronchoscopy revealed epidermoid carcinoma of the right main bronchus. Pneumonectomy was done in February 1948, and the patient was alive and well seven years later.





Specimen reveals emphysema of the right middle and lower lobes and a large tumor of the right main bronchus.

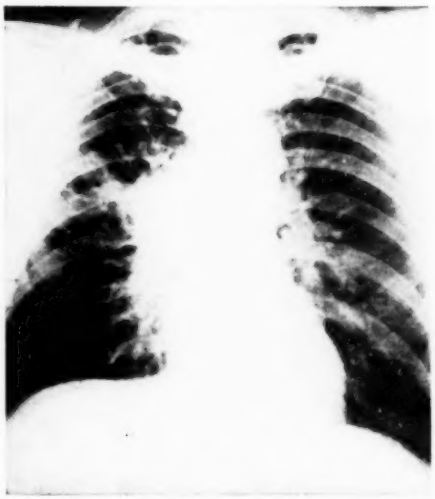


Small bronchogenic carcinoma of the squamous cell type causing fibroid pneumonitis of left upper lobe.

This 74 year old man had cough and fever at the time this x-ray was taken. Penicillin therapy brought partial relief of symptoms, but x-ray shadow persisted. He is still active seven years after left total pneumonectomy.

There is little evidence in these x-rays of bronchogenic carcinoma arising in the right upper lobe and invading the mediastinum, causing obstruction of the superior vena cava.

Appearance of patient shows evidence of vena caval obstruction. Note swelling of face and neck and dilatation of veins of upper chest and shoulders. Patient was obviously inoperable. X-ray therapy gave relief of symptoms, including signs of vena caval obstruction, and he led a normal life for more than two and a half years before advance of neoplasm caused death.



January 15, 1946. This 54 year old man complained chiefly of pain in his right shoulder. Exploratory thoracotomy disclosed a neoplasm arising in the right upper lobe bronchus which had invaded the phrenic nerve and lower trachea. Because of the extensive invasion, the lung was not removed. Biopsy revealed squamous carcinoma.

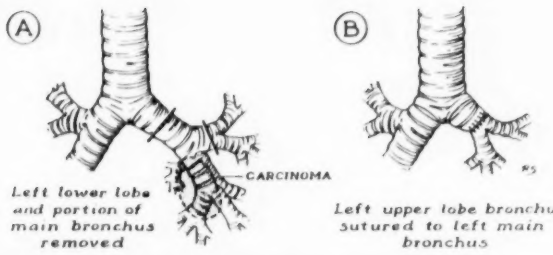
April 1, 1946. Two and a half months following x-ray therapy the hilar mass had almost completely disappeared. Later, a large abscess destroyed the right upper lobe. This man was still alive without signs of recurrence of this proved neoplasm seven years following exploration of the chest.

Specimen removed at left pneumonectomy on May 18, 1949 reveals an adenocarcinoma in the left upper lobe.

In May 1947, one year before admission to the hospital, this 71 year old man was told that he had a suspicious shadow in his left lung. In May 1948 he coughed up blood but had no other symptoms. An x-ray of the chest on May 5, 1948 revealed a large, soft shadow in and just above the left hilus.

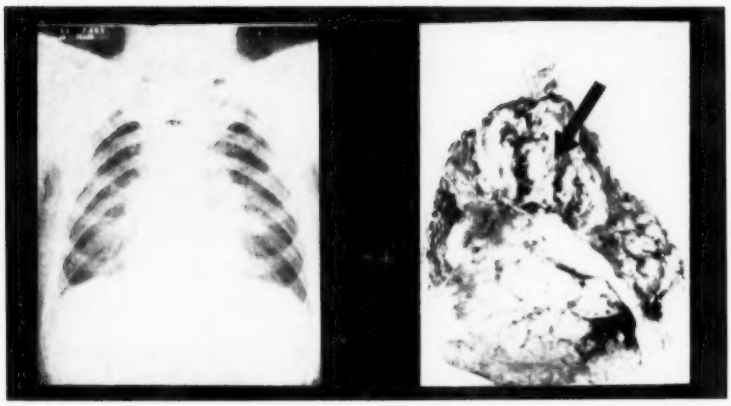
November 3, 1949. Patient complained of cough and hemoptysis. Chest x-ray revealed small shadow in the right lung. Bronchoscopic examination was negative.

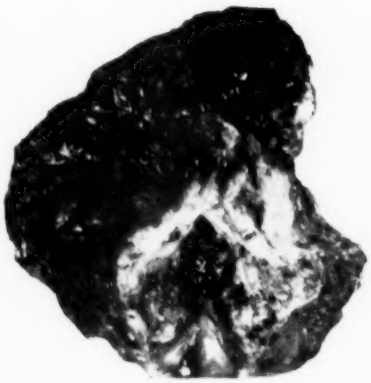
March 17, 1951. Cough and hemoptysis persisted for 18 months. X-rays revealed massive increase in size of shadow. Pneumonectomy was done in March 1951. The patient died nine months later from cerebral and peritoneal metastases.


A
B
CARCINOMA
Left lower lobe and portion of main bronchus removed
Left upper lobe bronchus sutured to left main bronchus

This 58 year old man had cough and hemoptysis of four months' duration. X-ray disclosed a lesion in the posteromedial segment of the left lower lobe, and emphysema of lower lobe.

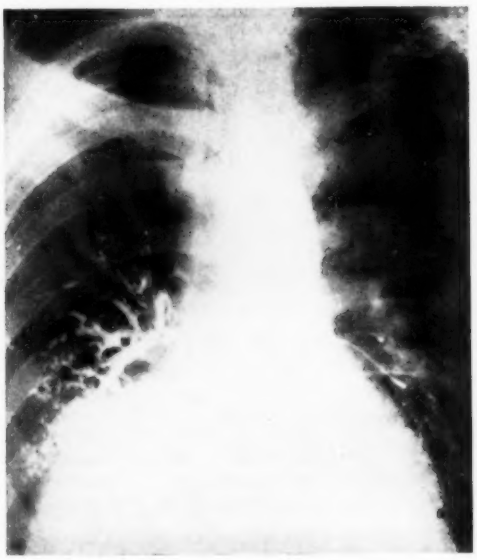
Specimen reveals epidermoid carcinoma extending along the left lower lobe bronchus. Additional length of bronchus obtained by resection of portion of left main bronchus.

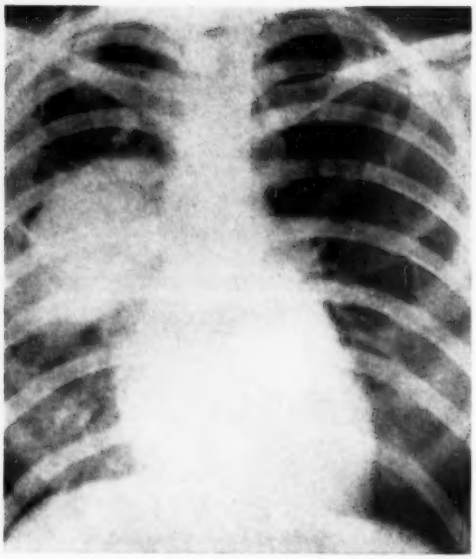


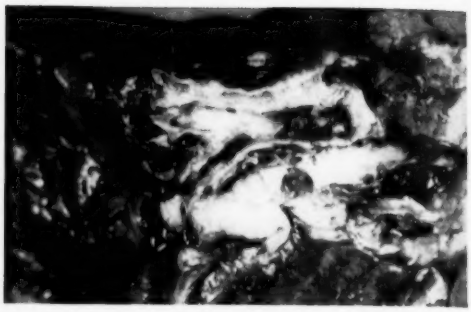


Bronchiectasis and abscess formation in the right middle and lower lobes secondary to epidermoid carcinoma of right main bronchus.

This patient had a long history of cough and fever. Bronchograms disclosed obstruction of the right lower lobe bronchus, a large mass invading the right lower lobe, and pneumonitis of the right upper lobe.

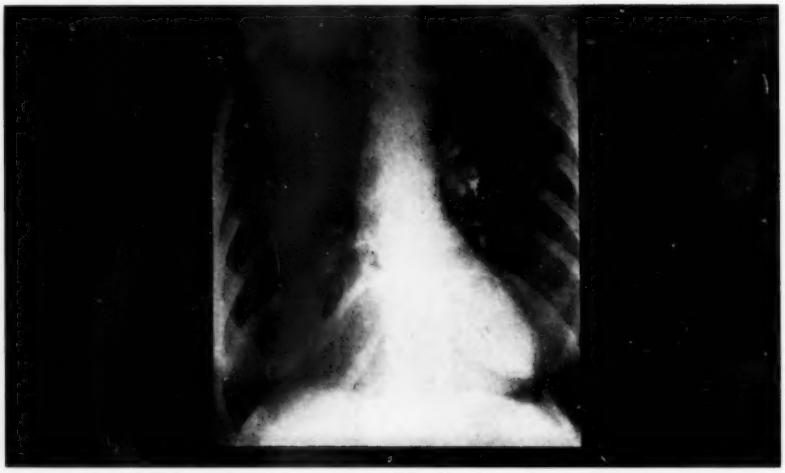






A highly anaplastic carcinoma invading the left anterior pulmonary vein.

A dense, sharply circumscribed shadow in the chest x-ray of a 28 year old woman. At exploration, this was found to be an anaplastic primary neoplasm which had invaded and extended along the anterior pulmonary vein to form a large tumor embolus in the left atrial chamber.



For three weeks before this x-ray was taken, this 64 year old woman noticed a streak of blood in a small amount of sputum she cleared from her throat each morning. An abnormal shadow was noted in the left upper lung field. The patient accepted readily the advice that she undergo exploratory thoracotomy. At operation, a small neoplasm was removed by resecting the anterior segment of the upper lobe. The patient is alive and well 10 years following the resection. Six years before this x-ray was taken, an early carcinoma of the cervix was detected and cured by radium therapy. Thus an intelligent patient, aided by her alert physician, has survived two separate primary carcinomas.

Respiratory Irregularities in Newborn Infants

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A. ROBERT BAUER

PHILIP J. HOWARD

EARLY descriptions of breathing in newborn infants which were based on simple inspection called attention to the characteristics of this age group, namely, the irregularities in rate, rhythm and amplitude of the individual respirations occurring in normal babies, as contrasted with the regular and more even breathing of older persons. These findings were later confirmed by means of a face mask type of spirometer which gave a permanent kymographic record of quantitative measurements of rate, tidal air, minute volume and general characteristics. However, this method had the disadvantage of disturbing the infant, which raised some doubt as to the findings being really basal. This disadvantage was fairly well eliminated by the development of a body plethysmograph, which was first used in normal newborn infants in the early 1930s by Murphy and Thorpe[1] and Deming and Washburn,[2] and in premature infants by Shaw and Hopkins.[3]

Figure 1 shows the body plethysmograph adapted from Deming[2] which was used in our studies. The infant's body is completely enclosed in the apparatus with the head protruding through a rubber collar so that he breathes atmospheric air (or whatever gas mixture we wished to administer by placing a cellophane tent over his head). The spirometer was attached directly to the plethysmograph and permanently recorded on a kymograph the volume of air moved by the actions of the chest and abdomen within the plethysmograph.

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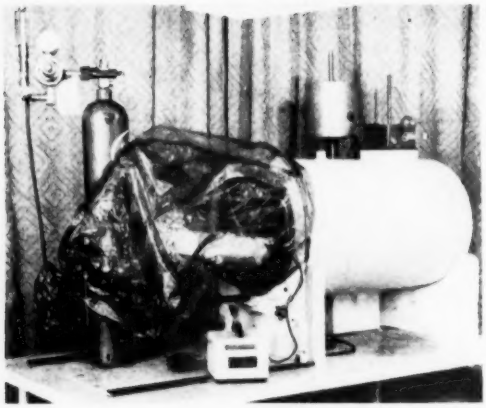

FIGURE 1. Body plethysmograph adapted from Deming, showing spirometer, kymograph, method of administering gas mixtures, and oximeter.

This volume equals that of air moving in and out of the respiratory tract and thus gives a faithful record of actual respiratory movements without disturbing the infant. This was believed to give truly basal results since the infant was sufficiently comfortable to sleep through the entire test—in fact, no tracing was considered acceptable unless the subject did sleep all through the test. Later improvements in this type of apparatus made by Bouterline-Young and Smith[4] in this country and by Kenneth Cross[5-7] in England have added much to the accuracy of the results.

The use of electronic systems in connection with a face mask by Miller[8-10] and by Goddard[11] and in connection with the plethysmograph by Drorbaugh[12] gave excellent results, and provided an improved method of study. We studied the movements of the chest and abdomen by means of pneumographic tracings and later combined this with simultaneous plethysmographic tracings using a purely mechanical system of recording. Miller[8-10] recently carried out a similar study employing an electronic system of recording which was very accurate.

Although periodic breathing is normal in the newborn infant, the appearance of periodic, or Cheyne-Stokes, breathing in an adult is very serious. In the adult, Cheyne-Stokes breathing is associated with cardiorenal failure, severe lung failure as in asthma or some types of pneumonia, or heart-failure. It occurs regularly in the anoxia of mountain sickness. Because the irregularity is so severe in adults it has been of great interest and studied in normal newborn and premature infants.

In the adult many factors increase or stimulate respiration. Some of the most important factors are oxygen deprivation from low oxygen atmosphere or disease; carbon dioxide excess, whether inhaled or metabolic; acidosis from administered acid or from metabolism; muscular exercise, either active or passive;

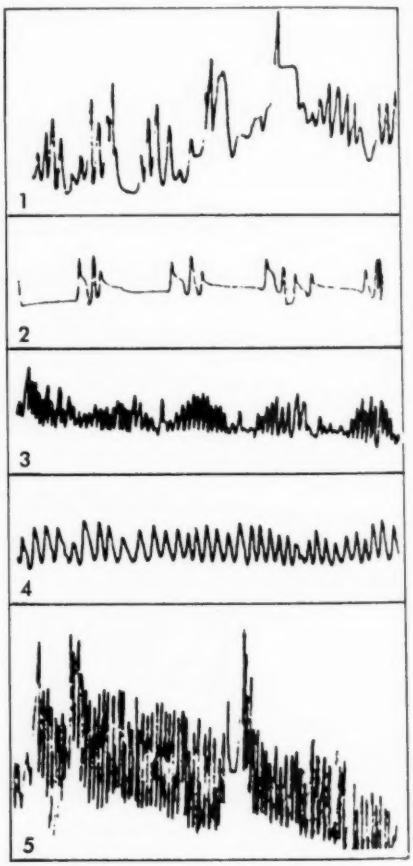

FIGURE 2. Breathing records for the immature, types I, II and III; the regular normal, type IV; and the stimulated, type V.

pressoreceptor reflexes from veins and arteries with rise in blood pressure; thermoreceptor reflexes from the hypothalamus; pain reflexes; psychogenic reflexes of an emotional nature, and voluntary control. In our work, and in most research in this field, these factors have been controlled as much as possible by taking records only during sleep. The first factor, low oxygen, as represented by 12.5 per cent oxygen in the respired mixture, usually has been found to act as a depressant in the early newborn period.

In the beginning of our studies with the plethysmograph, attention was directed to the types of irregularities encountered, and since there were several varieties, we classified them as shown in figure 2. The simultaneous tracings taken by the plethysmograph and by the pneumograph from the chest and abdomen showed that there was no greater efficiency in tidal air or minute volume when the chest and abdomen expanded together (positive phase) than when the chest retracted as the abdomen expanded (negative phase). Examples of each phase are shown in figures 3 and 4. Our interpretation of this phenomenon was that respiration was due chiefly to diaphragmatic action, with that of the chest being secondary and probably serving only as a good firm foundation from which the diaphragm could work. Figure 5, taken from Miller,[8-10] gives his interpretation of this phenomenon. He refers to the lack of co-ordination between the chest and abdomen as "seesaw," and feels that it is the normal type of action from the second to about the thirtieth day and is a sign of good diaphragmatic function, or intact vagal control. The important point in this respect is that lack of co-ordination between the chest and abdomen in newborns is normal, and that it is equally normal for the phase to change from positive to negative without any measurable change in the tidal air or the minute volume.[13]

We were interested in determining what effect the percentage of oxygen in the respired air would have on the irregularity of breathing and on changing the efficiency of respiration.* We administered mixtures containing

*Efficiency of respiration in our work has been judged by the minute volume. Efficiency of respiratory exchange, however, depends on the expansion of the alveoli, where the inspired gases are in closest contact with capillary blood. It is realized by us and has been carefully expressed by C. A. Smith and J. L. Wilson that occasional deep gasping respirations may accomplish more in alveolar dilation than we can demonstrate.

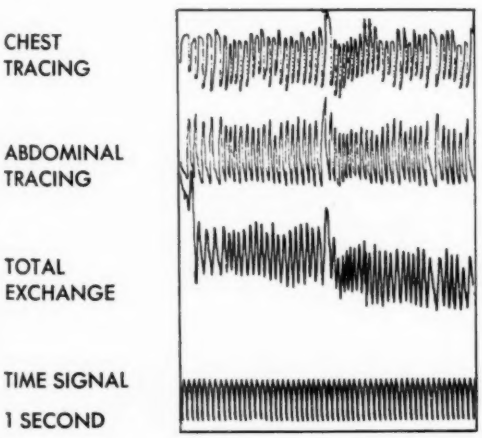

FIGURE 3. Breathing stimulated by carbon dioxide in the positive phase, with the chest and abdomen expanding together.

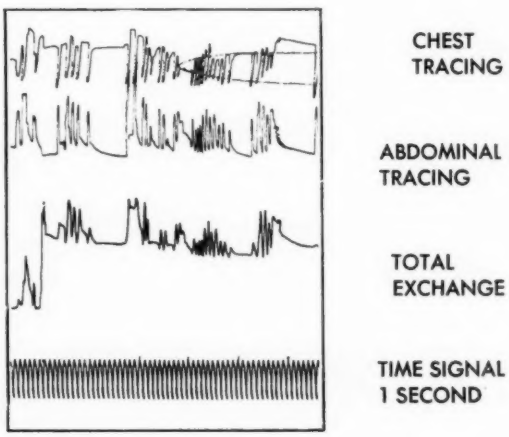

FIGURE 4. Breathing type I, irregular Cheyne-Stokes rhythm in low oxygen with a three second period of apnea. The phase is negative, with the abdomen contracted and the chest expanded. Gas analysis showed 11.75 per cent oxygen.

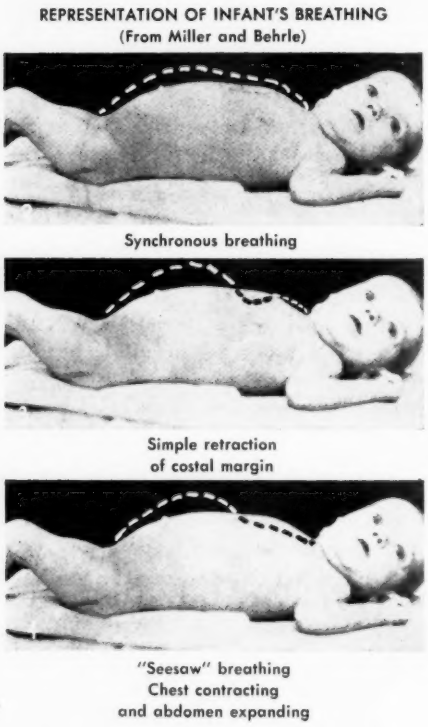

FIGURE 5. Chest and abdominal motion in breathing.

Reproduced courtesy of *Pediatrics*.

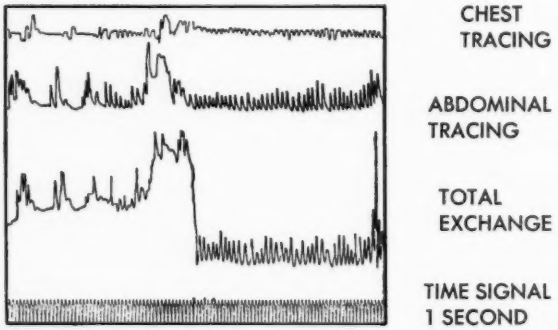

FIGURE 6. Breathing type I, irregular Cheyne-Stokes rhythm, becoming type IV, regular normal breathing, on administration of high oxygen concentration for 40 seconds. The phase is positive, with chest and abdomen expanding together.

Figures 3, 4 and 6 reproduced courtesy of *Am. J. Dis. Child.*—Howard and Bauer—May 1949.

from 12 to 90 per cent oxygen.[13] The use of 12 per cent oxygen converted regular breathing into periodic breathing in six out of nine infants.

When the infants were breathing irregularly, increasing the percentage of oxygen converted respiration to a regular type in 7 out of 10 cases (figures 6 and 7).[13] In certain cases there was a progressive increase in minute volume as the content of the mixture was changed from low oxygen to high oxygen to carbon dioxide. In all cases there was a great increase in minute volume with carbon dioxide, and in 18 of 20 cases there was a marked increase with high oxygen. Figure 8 illustrates this response in a five day old infant who was considered to be still in the immature phase of response, whereas figure 9 shows the response in a 25 day old infant which seemed to be changing from the immature type to the adult type.

Table 1 indicates the percentage of increase in minute volume obtained with various percentages of oxygen administered and is the

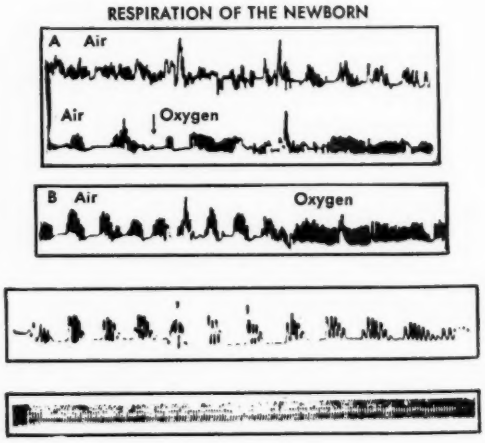

FIGURE 7. Effect of oxygen therapy on respiratory rhythm in premature infant.

Rhythm change from types I and II to type IV after administration of high oxygen mixture.

Rhythm change from type II with 12 per cent oxygen respiratory mixture to type IV with air.

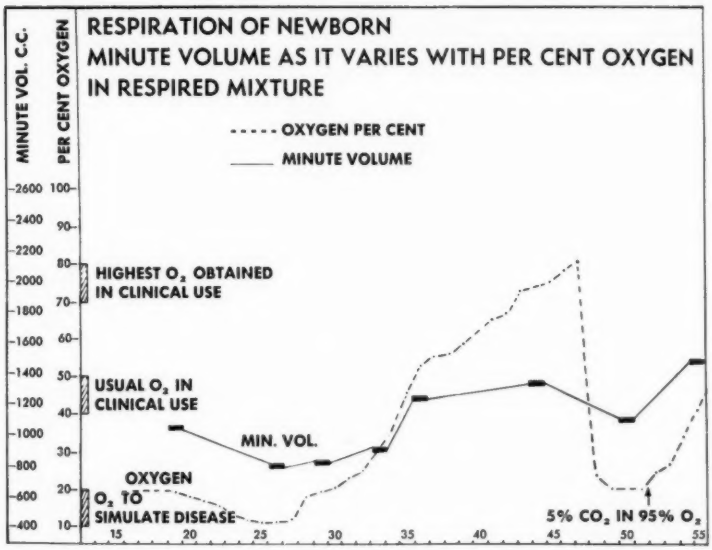

FIGURE 8. Increase in minute volume after administration of increased oxygen in respired mixture. Patient was a five day old infant, weighing 7 lb.; hemoglobin, 17 gm.; red blood cell count, 4.7 million.

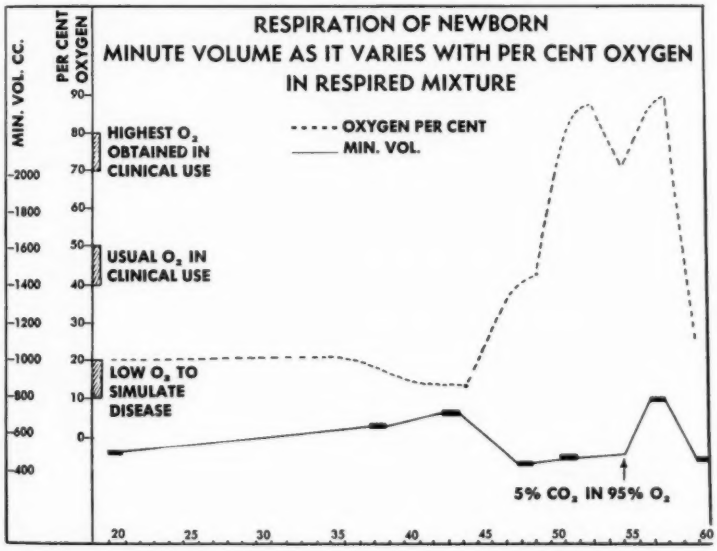
RESPIRATION OF NEWBORN
MINUTE VOLUME AS IT VARIES WITH PER CENT OXYGEN
IN RESPIRED MIXTURE
MIN. VOL. CC.
PER CENT OXYGEN
OXYGEN PER CENT
MIN. VOL.
HIGHEST O2 OBTAINED IN CLINICAL USE
USUAL O2 IN CLINICAL USE
LOW O2 TO SIMULATE DISEASE
5% CO2 IN 95% O2

FIGURE 9. Decrease in minute volume after administration of increased oxygen in respired mixture. Patient was 25 day old infant, weighing 14 lb. 12 oz.; hemoglobin, 16 gm.; red blood cell count, 4.9 million.

basis for our summary statement that 40 to 50 per cent oxygen increased the minute volume an average of 30 per cent.

The current explanation for periodic breathing accepted by most physiologists[14] is as follows: The neurons in the respiratory center are depressed by some factor such as anoxia, uremia, passive congestion, etc., resulting in a diminution in sensitivity to changes in carbon dioxide tension and pH of the blood. Pulmonary ventilation is thereby reduced and the arterial oxygen partial pressure falls below normal. Chemoreceptor reflexes then drive the respiratory center until the oxygen tension reaches normal. The reflex stimulation is then abolished, and since the carbon dioxide is re-

TABLE 1

MINUTE VOLUME VARIATION WITH LOW AND HIGH OXYGEN IN RESPIRED MIXTURE

CASE	BIRTH WEIGHT		AGE AT OBSERVATION (Days)	BLOOD		MINUTE VOLUME VARIATION		PER CENT OXYGEN IN RESPIRED MIXTURE
	Lb.	Oz.		Hemoglobin	Red Blood Count	Low Oxygen* (per cent)	High Oxygen† (per cent)	
1	7	0	5	17	4.7	−16	+ 32	74
2	6	7	7	11.5	2.7	−16	+ 54	53
3	4	7	27	14	4.4	−36	+ 22	42
4	6	2	11	15	4.9	−22	+ 15	56
5	7	0	8	15	3.9	−15	+134	67
6	5	8	14	...	...	−29	+ 19	56
7	4	15	23	15.4	4.7	−37	− 1.3	46
8	8	1	17	12.9	4.3	+ 8.8	+ 45	48
9	6	4	27	11	2.8	+53	+ 2	72
10	4	12	25	...	...	+ 3.4	− 15	40
						AVERAGE		
						−10	+ 30	

*Low oxygen as used here means the administration of 12 per cent oxygen in air, and checking the resulting mixture within the tent at one minute intervals with a Beckman oxygen analyzer to insure that concentration.

†High oxygen as used here means the administration of 90 per cent oxygen in air, and analyzing the resulting mixture within the tent at one minute intervals with a Beckman oxygen analyzer. The resulting percentages are given in the last column on the right.

duced by hyperventilation, apnea ensues and the cycle is repeated over and over until the original defect is corrected.

Because the administration of oxygen corrected periodic breathing in newborns, it was concluded that the respiratory center was depressed by anoxia. Cross[5-7] made out a strong case for this idea, supported by fine experimental work. He noted that administration of oxygen to newborn infants causes a depression of respiration for the first two minutes, followed by a secondary rise. This same reaction was reported by Miller.[8-10] The interpretation by Cross was that the oxygen at first eliminated the chemoreceptor drive, resulting in depression of respiration, but the oxygen returned the neurons in the respiratory center to a normal carbon dioxide sensitivity, giving the secondary rise. The second part of his work demonstrated that an infant who had been observed in anoxic atmospheres did not respond to carbon dioxide stimulation to the same degree that he would in air, which Cross concluded was proof of the depressing effect of anoxia on the sensitivity of the respiratory center. The chief objection to this conclusion is that in the textbook explanation of periodic breathing[14] it was stated that the administration of oxygen would cause apnea by abolishing the chemoreceptor drive—this is the opposite effect to that observed in newborns. The one exception to this in adults is in the case of chronic anoxic hyperventilation occurring in persons acclimated to high altitudes. In this instance both carbon dioxide and oxygen blood tensions are low, but the administration of oxygen does not cause apnea as it does when administered in acute anoxia; the implication is that the respiratory center threshold has been set at a lower level during acclimation.

The explanation just stated would fit the situation found in newborns, for Wilson and his group[15] have shown that both carbon dioxide and oxygen tensions are low in newborn infants. The administration of oxygen does not cause apnea but actually abolishes periodic breathing, if present. The explanation for this would seem to be that the partial anaerobic existence of newborns, as postulated by Wilson,[15] results in the production of insufficient amounts of carbon dioxide to stimulate the respiratory center, and the administration of oxygen increases the production of carbon dioxide which in turn stimulates the respiratory center and increases ventilation. The fact that pH shares equally with carbon dioxide as

a stimulant of the respiratory center and may act independently of carbon dioxide gives it an important position in any consideration of respiratory regulation. While it is true that carbon dioxide tension and pH vary inversely, it is also true that other factors, such as organic and inorganic acids, can contribute to an uncompensated acidosis that will affect regulation of breathing. The newborn has been shown by Wilson and co-workers[16, 17] to be in a state of uncompensated acidosis and yet not hyperpneic. This also suggests that the respiratory center threshold has been set at a lower level.

As a possible explanation for the factual information obtained from our experiments and those of other investigators, we suggest that these findings represent only a small part of a finely balanced set of regulatory functions for the respiratory system, rather than a complete regulation in itself, based entirely on a carbon dioxide and oxygen exchange predicated on abnormal conditions existing before and after birth. If one thinks of the many factors which go into the thermostatic regulation of heat in his home, one can see how the more complicated physiologic regulation of respiration in the newborn may be influenced by a multiplicity of factors, rather than by one or two isolated factors. We also considered the possibility these seemingly paradoxical situations might be part of a protective mechanism to help the infant during the transition period from relative immaturity to a more stable adult type of existence, rather than a significantly pathologic process. For example, the polycythemia and peculiar type of fetal hemoglobin present at birth make for better oxygen transport, and this, together with the partial anaerobic existence, results in the newborn's well-recognized resistance to anoxia. Since a lowered respiratory threshold permits him to tolerate a lowered pH, and the lowered carbon dioxide tension allows him to accept a sizable increase in carbon dioxide tension, it would seem to follow that this, plus resistance to anoxia, serves as some measure of protection against an interruption of respiratory function either in utero or after delivery.

If the postulate given here is accepted as a working theory, it becomes evident that irregularity of breathing per se in a newborn infant is not an indication for drastic therapeutic measures. The decision to use oxygen therapy or medicinal stimulants should be made on the basis of a general appraisal of such factors as cyanosis, feeble heart action, shock, weak cry, and lack of response to stimulation, in addition to a consideration of the type and efficiency of respiration. Also, we have tried to show that administration of 40 per cent oxygen will accomplish as much as higher concentrations in stimulating respiration. This is becoming a matter of great importance, for evidence is accumulating rapidly to indicate that toxic results of oxygen administration, such as retrolental fibroplasia and pulmonary irritation, occur from concentrations higher than 40 to 50 per cent.

REFERENCES

1. Murphy, D. P. and Thorpe, E. S., Jr.: Breathing measurements on normal newborn infants. J. Clin. Investigation 10:545-558 (August) 1931.
2. Deming, J. and Washburn, A. H.: Respiration in infancy. I. Method of studying rates, volume and character of respiration with preliminary report of results. Am. J. Dis. Child. 49:108-124 (January) 1935.
3. Shaw, L. A. and Hopkins, F. R.: Respiration of premature infants. Am. J. Dis. Child. 42:335-341 (August) 1931.
4. Bouterline-Young, H. J. and Smith, C. A.: Respiration of full term and of premature infants. Am. J. Dis. Child. 80:753-766 (November) 1950.
5. Cross, K. W.: Respiratory rate and ventilation in newborn baby. J. Physiol. 109:459-474 (September 15) 1949.
6. Cross, K. W., Hooper, J. M. and Oppe, T. E.: Effect of inhalation of carbon dioxide in air on the respiration of the full-term and premature infant. J. Physiol. 122:264-273 (November 28) 1953.
7. Cross, K. W., Hooper, J. M. and Lord, J. M.: Anoxic depression of the medulla in the new-born infant. J. Physiol. 125:628-640 (September 28) 1954.
8. Miller, H. C. and Behrle, F. C.: Respiratory patterns in newborn infants as determined by airflow and pneumographic studies and their possible relationship to deficient vagal mechanism. Pediatrics 10:272-284 (September) 1952.
9. ———: Changing patterns of respiration in newborn infants. Pediatrics 12:141-150 (August) 1953.
10. ———: Effects of hypoxia on the respiration of newborn infants. Pediatrics 14:93-103 (August) 1954.
11. Goddard, R. F., Clark, J. and Bennett, V. R.: Newer concepts of infant resuscitation and positive pressure therapy in pediatrics. Am. J. Dis. Child. 89:70-97 (January) 1955.
12. Dornbaugh, J.: Method for study of ventilation in small infants. Am. J. Dis. Child. 88:808 (December) 1954.
13. Howard, P. J. and Bauer, A. R.: Irregularities of breathing in the newborn period. Am. J. Dis. Child. 77:592-609 (May) 1949.
14. Pitts, R. F.: Regulation of respiration. In Howell, W. H.: Textbook of Physiology. Edited by John F. Fulton. Ed. 16. Philadelphia, W. B. Saunders Company, 1949, p. 844.
15. Wilson, J. L., Reardon, H. S. and Murayama, M.: Anaerobic metabolism in newborn infant; on resistance of fetus and newborn to oxygen lack. Pediatrics 1:581-592 (May) 1948.
16. Graham, B. D., Reardon, H. S., Wilson, J. L., Tsao, M. U. and Baumann, M. L.: Physiologic and chemical response of premature infants to oxygen-enriched atmosphere. Pediatrics 6:55-71 (July) 1950.
17. Graham, B. D. and Wilson, J. L.: Chemical control of respiration in newborn infants. Am. J. Dis. Child. 87:287-297 (March) 1954.

Management of Benign Prostatic Hypertrophy

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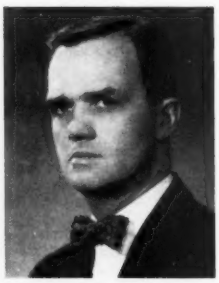

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THE cause of benign prostatic hypertrophy remains unknown despite intriguing research by a number of investigators. With advancing years man generally and specifically undergoes some degree of atrophy of skeleton, muscle, skin and most organs. It is paradoxical, then, that the prostate undergoes enlargement in some 35 to 60 per cent of men over 50 years of age.

As fortunately only about 15 per cent of cases of obstructive prostatism require surgery, the first problem is to determine accurately which cases do require operative intervention. The decision to excise surgically the enlarged gland often must be individualized, and specialized training and experience are of value in making these decisions. However, there are certain fundamental positive and negative criteria that apply to all patients with obstructive prostatism which will assist the general practitioner in deciding whether or not the patient should be referred to a urologist for operation. The second area of interest for the general practitioner is that of postoperative management. It is only natural that most general practitioners have little interest in the technical aspects of the surgery. Actually, surgical procedure is but one phase in the treatment of obstructive prostatism. Regardless of the fact that for most of these patients the hospital stay is relatively short the total postoperative recovery period may be prolonged. The referring physician should be familiar, therefore, with the usual postoperative course in such cases and should have a basic concept of the operation in order to understand and properly manage these patients postoperatively. It is the purpose of this paper to discuss these and other aspects of the problem as they apply to the family physician.

To establish a correct perspective from the onset, it should be stressed that surgical excision of a benign hypertrophied prostate is never an emergency procedure. For numerous

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reasons, excision is frequently strongly indicated, but it should always be viewed as an elective operation. Per contra, providing urinary drainage in a patient with obstructive prostatism is often an emergency requiring urethral catheter drainage or, rarely, suprapubic cystotomy. The disassociation of these two principles is occasionally overlooked in cases of nearly complete urinary retention produced by an obstructive hypertrophied prostate. Failure to apply these concepts causes many unnecessary deaths from prostatic surgery each year.

Preoperative Considerations

Evaluation of symptoms—Prostatic hyperplasia produces signs and symptoms at an advanced age when there frequently are associated degenerative diseases of the liver, heart, blood vessels or kidneys. It is the prime function of the physician to evaluate, treat and return these patients to their families in the best possible condition. Occasionally an associated condition, such as a recent myocardial infarction with residual angina pectoris, will preclude prostatic surgery, in order not to jeopardize life by an elective procedure. True, a few patients in this group may not like constant catheter drainage of urine into a rubber bag strapped to the thigh under the trousers. Regardless, at least they are alive to complain about it, and there is always the possibility that their physical condition may later improve and make surgery possible.

As the total patient must be evaluated, and not just the urologic tract, any associated condition, such as progressing hypertension, may well influence the physician to recommend surgery for a gland which per se does not necessarily require surgery at present. The reasoning in such a case is that the patient probably will never be in better condition than at present, and if surgery is delayed it may have to be performed later when the patient is a poorer operative risk. If no such generalized condition coexists, however, and immediate prostatic surgery is not recommended, the patient should be examined in the office approximately twice yearly. At those times further anatomic enlargement of the prostate may be determined and progression of symptoms noted. Most physicians check for residual bladder urine. The urine should be examined for evidence of infection and the blood urea nitrogen or nonprotein nitrogen determined. In this connection, it should be pointed out that a nonfasting or casual sample of blood for either of these tests is adequate for simple clinical evaluation of renal function.

The patient with only minimal to moderate benign enlargement of the prostate, with few symptoms of urinary obstruction, and no renal damage or infection presents a problem that must be individualized. For example, some patients do not mind getting up two or three times at night to void. Diurnal frequency of every two hours and some decrease in the caliber of the urinary stream may cause such patients no subjective concern or annoyance. Another patient with the same degree of prostatic enlargement may be distressed greatly by these symptoms. He may be unable to resume sleep after nocturia. All else being equal, subjective reaction to symptoms of obstructive prostatism may present insufficient or sufficient indications for prostatic surgery. If the presenting signs or symptoms do not warrant operative intervention, the patient should be advised that he probably will require surgery later if the prostate continues to enlarge and further occludes the urethra.

A few patients develop no symptoms other than those mentioned as a result of obstruction and never require surgery. As a general rule the patient consults his physician and undergoes prostatic surgery only for aggravating or distressing alterations of the voiding mechanism consisting of at least two of the following symptoms: frequency, urgency or hesitancy, dysuria, decrease in caliber and force of the urinary stream, occasional hematuria, terminal dribbling, etc.

Rectal examination—It has been stated previously that, depending on the source consulted, some 35 to 60 per cent of men over 50 years of age have prostatic hypertrophy. Routine rectal examination of healthy men in this age group or regular attendance by the physician at autopsies performed on elderly men who died from nonurologic causes will con-

FIGURE 1. Intravenous pyelogram revealing large prostatic hypertrophy indenting the floor of the bladder. Size of prostate was confirmed by rectal examinations. There was no infection or renal damage and only minimal symptoms of obstruction. Surgery was not indicated.

firm these statistics. Most older men, therefore, adjust physiologically to an enlarged prostate and do not require surgery. Regardless of how large a hypertrophied prostate may feel on rectal examination, operative removal is not necessary unless the patient cannot adjust or unless there are symptoms of urinary obstruction, infection or renal damage (figure 1). Simple anatomic enlargement of the prostate does not indicate operation.

From the other standpoint, it may be questioned whether prostatic surgery ever is indicated, if rectal examination reveals a normal-sized prostate. When the prostate undergoes hyperplasia it usually enlarges in all directions and can be palpated by rectal examination. In certain instances, however, a small hyperplasia of only lateral or median lobes may cause considerable intra-urethral pressure. In other patients, median bar hypertrophy may result in bladder neck obstruction and cause complete urinary retention. In either case, the prostate may be nearly normal to palpation; however, if lateral lobe or median bar hypertrophy produces symptoms of urinary obstruction, infection or renal damage, surgery is indicated.

Most patients with symptoms of obstructive prostatism have a large prostate on rectal examination. The gland is usually, but not always, symmetrically enlarged and the median sulcus is palpable. In addition to backward projection of the prostate, the finger should be moved laterally and also vertically in order to palpate width and supero-inferior limits of the hypertrophy. The consistency of a benignly hypertrophied prostate resembles that of an artgum eraser. While any area of localized increased density may be a small prostatic adenoma, an area of fibrosis, infarction, prostatic calculus or a tuberculous lesion, the possibility of early prostatic cancer should not be excluded from the differential diagnosis.

Prostatic cancer coexists with benign prostatic hypertrophy in some 10 to 20 per cent of patients. Specialized examination and biopsy are indicated under these circumstances. In fact, any localized area of increased density (whether or not it is a nodule) in the normal-sized or enlarged prostate should be considered to be early prostatic cancer. Over 85 per cent of prostatic cancers begin in the posterior lobe, which is the area palpated on rectal examination. The burden of proof rests with the physician who states that a prostatic nodule is not malignant. Statistics lend emphasis to this comment: In over 90 per cent of patients referred to the urologist with prostatic cancer, malignancy already has spread beyond hope of cure. In patients in whom the lesion has not metastasized, total prostatectomy offers a 38 to 50 per cent cure rate.

Catheterization for residual urine and complete obstruction—The patient with bladder neck obstruction compensates by developing hypertrophy of the bladder wall. The bladder capacity may remain normal or decrease. As the obstruction increases, the bladder musculature must work harder in order to expel urine. If the bladder becomes hypertrophied enough, it is possible to have an enormously

enlarged prostate without developing any residual urine. This can and does occur. Most patients, however, develop detrusor compensation to a certain degree; further increase in the bladder neck obstruction will cause the bladder musculature to become inadequate. It is at this time that residual urine develops in the decompensating, dilating bladder.

Most urologists use measurement of residual urine to determine the degree of compensation of bladder hypertrophy for a bladder neck obstruction. Many patients with bladder hypertrophy have a marked tendency to develop cystitis. Residual urine should be obtained by catheter only while using strict aseptic technic. After voiding, the normal bladder should contain less than 5 cc. of urine.

A marked increase in residual urine over a six month period usually indicates that bladder compensation is failing rather rapidly and that prostatic surgery will be necessary in the not too distant future. Regardless of the size of the prostatic hypertrophy or the extreme degree of associated infection and symptoms of obstruction, if no residual urine is present there is usually no appreciable renal damage. Conversely, it may be stated that in patients with only minimal enlargement of the prostate, as noted by rectal examination, with no infection and with only mild symptoms of obstruction, there may be serious renal damage if a large amount of residual urine (over 100 to 200 cc.) is present.

I do not use residual urine determinations in evaluating patients with benign prostatic hypertrophy. It is contended that the precise amount of residual urine is not of any great value in selecting treatment. The patient with a large amount of residual urine has marked symptoms of obstructive prostatism—usually in proportion to his prostatic enlargement—and will therefore require treatment. Consequently, determination of the amount of residual urine does not appear indicated, and if performed, occasionally may cause cystitis.

Inability to catheterize the patient with acute retention due to benign enlargement of the prostate is usually due to errors in technic and to ill-advised choice of catheter. The male urethra has the form of an "S" curve. If the penis is lifted straight up from the recumbent patient and held under slight tension at a right angle to the legs and abdomen, one curve of the "S" is eliminated. When a well-lubricated catheter is gently inserted into the urethra, it should be introduced freely to the point of obstruction and then pushed firmly 1 to 2 cm. at a time until it has passed the obstruction. In more resistant cases, the passage of a curved metal sound prior to using the catheter frequently furnishes the physician with some preliminary information concerning urethral anatomy and location and degree of obstruction. If possible, a Foley catheter with a 5 cc. bag should be used, because the catheter should be left indwelling. Enlargement of a median bar or middle lobe of the prostate is difficult to overcome with the simple, straight catheter. The two leading manufacturers of catheters have, therefore, marketed a Foley bag catheter with a stiffened and slightly curved tip to override these obstructions. Many physicians attempt to pass catheters that are too large for the caliber of the urethra at the point of obstruction, while others use catheters so small that they fail to pass due to buckling of the thin rubber tube within the urethra. No. 18 and No. 20 French catheters appear to be easiest to introduce in most patients. The use of a stylet or mandrin by inexperienced persons is inadvisable, as it often results in urethral tears or perforations.

If, after a reasonable period of time, it has been impossible to catheterize the patient it is best to desist and to seek specialized assistance. If there is too much urethral trauma it may be impossible for the urologist to catheterize the patient, and an unnecessary emergency operation may have to be performed to provide urinary drainage.

If the patient has had incomplete chronic urinary retention for a long time and suddenly develops complete retention, some believe that it is not advisable to empty the bladder rapidly after the catheter is inserted. The sudden pressure imbalance at the tubular and glomerular level may result in serious renal injury. The first 100 cc. of urine should be drained off at the rate of 5 cc. every 5 to 10 minutes and the remainder emptied freely.

As the catheter is to be left indwelling, a broad-spectrum antibiotic should be used regardless of the presence or absence of urinary infection. Catheters are foreign bodies that tend to promote cystitis and urethritis. They are a necessary evil. GANTRISIN®, 1 gm. four times a day, is useful and inexpensive in reducing the incidence of infection. Prior to any basic therapy the status of the upper urinary tract should be determined. A urea clearance or two hour phenolsulfonphthalein test or at least a nonprotein nitrogen determination must be obtained.

Cystitis—Patients with benign prostatic hypertrophy tend to develop cystitis. Some patients with bladder neck obstruction also develop a vesical calculus or diverticulum. Cystitis aggravates existing vesical irritability and produces an increase in many symptoms already present as part of the complex of obstructive prostatism. Patients with considerable obstruction who acquire acute cystitis may develop complete urinary retention and require use of an indwelling urethral catheter.

Most patients with prostatic enlargement who have cystitis should have the voided urine collected for culture and sensitivity studies. The penis must be washed well with soap and warm water, followed by application of a mild antiseptic solution. The first ounce or two of urine voided is discarded and then some of the specimen collected in a sterile container. Before obtaining the laboratory report of the urine culture, the trial use of a broad-spectrum antibiotic is certainly advisable. These infections usually are due to some gram-negative organism, and the clinical guess concerning the antibiotic already prescribed frequently is accurate when compared with the sensitivity study. Contrary to popular usage, I believe that cystitis is an infection of not only the urine but also of the bladder wall. As a consequence it is recommended that tissue, and not urinary, level doses of antibiotics or chemotherapeutic agents be used.

It is possible to effect remission of cystitis secondary to an enlarged prostate, but it will invariably recur unless the cause (the prostate) is removed. The development of recurrent or persistent bladder infection in a patient with benign prostatic hypertrophy is usually a definite indication for surgery. Prior to surgery constant catheter drainage and administration of the appropriate antibiotic are frequently necessary to control a resistant, severe cystitis.

Cystoscopy—Many urologists do not believe that preoperative cystoscopy is necessary. The principal objection to the procedure is that it may cause cystitis. I use cystoscopy routinely in all patients who are to be operated. Benign prostatic hypertrophy occurs in the same age group as bladder cancer. Cystoscopy occasionally will reveal that while the patient does have an enlarged prostate on rectal examination, his symptoms are produced by a cancer of the trigone of the bladder. Rectal examination provides approximate data concerning posterior enlargement of the prostatic adenoma. Panendoscopy reveals the degree of anterior and intravesical extension of the gland. Both examinations are necessary

FIGURE 2. Cystogram demonstrating two diverticula of the bladder resulting from median bar hypertrophy.

to determine the type of prostatic operation indicated. It is not enough to elect transurethral resection on the basis of a small amount of hypertrophy determined by rectal examination. Cystoscopy may reveal a diverticulum of the bladder (figure 2) or a large intravesical enlargement of the prostate that should be excised suprapubically. It may also show a large vesical calculus that could not be crushed with a lithotrite at time of transurethral prostatectomy (figure 3).

Intravenous pyelograms—While it would be highly desirable to have an intravenous pyelogram of every patient requiring surgery for obstructive prostatism, it is absolutely necessary only in certain selected cases. Moreover, the additional expense of intravenous pyelography must be considered. If the history suggests a renal calculus in addition to prostatic hypertrophy, then a pyelogram should be taken. Pyelograms are of value in uremic patients when the nonprotein nitrogen is not over about 60 mg. per cent. If the nonprotein nitrogen is over 60 mg. per cent, DIODRAST® clearance by the tubules is so poor that the contrast medium will not be visible roentgenographically. Patients recovering from uremia by catheter drainage should always have an intravenous pyelogram as soon as the uremia subsides to determine the degree of hydronephrosis or ureteral dilatation.

Renal damage—Any increase in blood-urea or nonprotein nitrogen concentrations in a patient with obstructive prostatism usually indicates a large quantity of residual urine and mandates constant indwelling catheter drainage and treatment of infection, if present. Many patients with renal damage secondary to prostatic hypertrophy have incompetent ureterovesical valves, while others fail to have normal ureteral drainage because of prolonged increased intravesical pressure (figure 4). In either case, the increased pressure of intraurethral urine is transmitted to the renal pelvis and calyces. This increase in urine pressure is then transmitted up the tubules to the glomeruli. Fortunately in most patients with renal damage due to this etiologic factor, constant urinary drainage via urethral or suprapubic catheter may cause a reversal of a great proportion of this renal tubular and glomerular damage. A few of these patients will have a varying residual of irreversible renal injury. Surgery performed prematurely during the period of recovery from reversible renal damage often may be fatal. It is all the more tragic because such deaths are preventable. Once the indwelling catheter is inserted and the infection treated, the usual course is merely a matter of waiting for renal recovery. This may be measured by a two hour phenolsulfonphthalein excretion or by blood nonprotein nitrogen determinations. I prefer the urea clearance test; it is so sensitive that with renal damage producing a urea clearance of 20 to 40 per cent, the blood urea nitrogen may still be within normal concentration. This period of waiting may require from less than a week to several months. The working rule of most surgeons is that once renal function studies reveal fixed improvement, and if the patient appears moderately well clinically and is not

FIGURE 3. Large vesical calculus secondary to benign prostatic hypertrophy.

FIGURE 4. Cystogram producing bilateral nephro-ureterograms due to incompetency of the ureterovesical valves, caused by benign prostatic hypertrophy and increased intravesical urine pressure.

anemic, surgery may be performed with safety.

It is my experience, however, that an exception should be mentioned to this rule of thumb. For example, if renal function is measured by the rather crude method of serum nonprotein nitrogen concentration, and it decreases from a high concentration but remains fixed at 85 mg. per cent or above, some 25 per cent of patients in this category will die from renal insufficiency one to four months postoperatively. If there is so much glomerular damage that the nonprotein nitrogen remains fixed at this high concentration, then there also is associated severe tubular damage. These tubules often are unable to properly handle chlorides, potassium, sodium and conservation of base. In fact, the fatal cases have usually been primarily electrolyte problems, sometimes associated with acidosis and always with a slowly climbing nonprotein nitrogen. It is imperative, therefore, that this type of patient be evaluated for serum electrolyte, carbon dioxide-combining power and tubular function before he is informed that operation is indicated. If alterations of these components are correctable and remain stabilized by appropriate intravenous solutions, and if there is no anemia, then surgery usually may be performed without too great a risk to the patient. On the other hand, if intensive, prolonged attempts at correcting electrolyte or acid-base abnormalities by appropriate treatment are unsuccessful, and if anemia persists after repeated blood transfusions, surgery of the prostate is definitely contraindicated, and the patient should be discharged from the hospital with a permanent indwelling catheter. Reevaluation of total renal function should be repeated in six months or a year.

To indicate the gravity of renal damage secondary to prostatic hypertrophy, Davis[2] reported a 22 per cent preoperative mortality rate in ward patients under his care in 1937. Gailbraith[1] reported a 20 per cent mortality rate in a similar group of patients in 1949. In 1953, Davis[2] reported that the preoperative mortality rate was zero among 450 private patients. In the last consecutive series of 506 private and ward patients under my care from 1951 to 1954, there was no preoperative mortality. This favorable status has been obtained by appreciating the importance of preoperative urinary drainage, applying newer concepts of fluid and electrolyte balance, generous use of whole blood, and modern antibiotic and chemotherapeutic agents.

Therapy

Prostatic massage, urethral dilatation and estrogens—No clinical evidence has been reported to indicate that pressure, by either prostatic massage or dilatation of the prostatic urethra with a sound, effects reduction of an adenoma or permanently relieves symptoms of obstructive prostatism. While it has been reported that use of estrogens will occasionally produce slight diminution of symptoms of benign hypertrophy, results invariably are inadequate and fall disappointingly short of the desired goal. Use of estrogens is not recommended.

Type of prostatic surgery—Urologists should be able to perform all four types of prostatectomy—(1) transurethral, (2) suprapubic, (3) retropubic and (4) perineal. The route of approach depends on the size and precise location of the enlargement. Most urologists use the transurethral method for median bar hypertrophy and hypertrophied prostates weighing under about 40 gm. Larger prostatic adenomas are removed by one of the three open enucleative procedures. The selection of a particular open method frequently is based on the background and experience of the surgeon, or on the location (intra-urethral or intravesical) of the greatest part of the gland. Most urologists do not use the perineal approach for anything other than total prostatectomy for early prostatic cancer. When this approach is used for large benign enucleations there is a greater risk of incontinence or impotence than there is with either the suprapubic or retropubic route. Most urologists do not use retropubic prostatectomy on markedly obese subjects due to technical inconvenience. Suprapubic prostatectomy has few disadvantages, the greatest being the prolonged postoperative hospital stay necessitated by this type operation. Replacement transfusions are mandatory in elderly patients who can little afford myocardial or cerebral anoxia of any degree.

The important concept is that regardless of which method of prostatectomy is used, all the adenoma must be removed. This applies particularly to certain popular misconceptions concerning transurethral resection. In this operation, not just enough of the adenoma is removed to provide an adequate tunnel for voiding, but it must be excised down to the prostatic capsule. Anything less than a complete resection down to the capsule subjects the patient to possible long-standing infection or subsequent prostatic surgery when the residual adenoma increases in size. The single exception to this principle is the quick tunneling resection reserved for patients who are very poor surgical risks. Furthermore, when it is stated that the patient has undergone prostatectomy for benign hypertrophy of the prostate, it should be understood that *adenectomy* is implied, for the entire prostate is not removed. The hypertrophied prostate is enucleated down to the capsule. This capsule is composed of compressed nonadenomatous prostate. True prostatectomy with total excision of the prostate and seminal vesicles and anastomosis of the urethra to the bladder is performed for early malignancy of the prostate, not for benign hypertrophy.

Postoperative Complications and Considerations

Epididymitis—The incidence of epididymitis is considerable following the various types of prostatic surgery. It may be reduced by at least two-thirds (to 1 to 3 per cent) if bilateral vasectomy is performed prior to surgery or an indwelling urethral catheter is inserted preoperatively.

Impotence—Impotence may occur in a small percentage of patients following any one of the four types of prostatic surgery, but its incidence is exceedingly small. Patients with perineal enucleations run the greatest risk of impotence, according to Rowe and Kimbrough[3] and others.

Incontinence—This complication should not occur unless the external urethral sphincter is injured during removal of the prostate.

Urethral stricture—Urethral stricture occurs most frequently after transurethral resection of the prostate and may require regular monthly dilatations for a year or more.

Sterility—Most prostatic surgery damages or actually removes the internal urethral sphincter. During ejaculation, therefore, all the semen regurgitates into the bladder. Perforce, most patients having bladder neck surgery are rendered sterile. Unless absolutely necessary, therefore, bladder neck surgery is contraindicated for younger patients with median bar hypertrophy or contracture of the bladder neck.

Infection—Every patient with enucleation of a hypertrophied prostate has postoperative infection of the urine as a normal result of the operation. This applies particularly to cases in which the transurethral method is used. The infection frequently persists for one to four months. To understand the reason for

this infection it is necessary only to consider that for several months the patient has had a large, denuded prostatic fossa. This fossa is raw—not covered by epithelium. In addition to being constantly wet with urine, which delays re-epithelization, another variable has been introduced, namely, infection. Many of these patients have preoperative cystitis, which is intractable, because the cause of infection (the prostate) has not been removed. The infection persists and involves the prostatic bed postoperatively. An additional cause is the urethral catheter used frequently before, and routinely after, surgery. While the catheter is necessary to divert the urine, it acts as a foreign body which contributes to or causes infection of the prostatic fossa. Treatment of the infection should be persistent. As this infection may cause symptoms similar to obstructive prostatism, the reparative process involved should be explained to the patient. If complete adenectomy was performed, the infection will always be cured.

Prognosis

With attention to the few principles mentioned, the mortality rate from prostatic surgery no longer is high; it is, in fact, one of the lowest for any type of major surgery, geriatric or otherwise. For private patients at the Mayo Clinic the mortality rate for transurethral resection was reported to be 1.1 per cent;[4] for ward and private patients at the University of Minnesota the rate reported is 1.2 per cent,[5] and Nesbit[6] in 1946 reported a mortality rate of 1.8 per cent for this same type of prostatic operation. Using the retropubic approach, Moore[7] reported a rate of only 1.7 per cent. Even prior to use of antibiotics, Young[8] in 1926 had only a 3.2 per cent mortality rate with perineal prostatectomy. I had a 0.6 per cent mortality rate in a series of 180 consecutive suprapubic enucleations. For all types of prostatectomy (506 patients) our mortality rate is 1.5 per cent, which is approximately what may be expected in most university hospitals adhering to the principles discussed in this paper. Operative deaths are usually due to myocardial infarction, pulmonary embolus or cerebrovascular accidents.

Summary

Establishing urinary drainage may be an emergency procedure, but surgery for prostatism is always an elective operation. The benign hypertrophied prostate is never excised simply because it is enlarged; there must be associated aggravating or distressing alterations in micturition, or infection or renal damage.

The mortality rate from prostatic surgery has been reduced to 1 to 2 per cent because of: modern drugs in treatment of infection; application of knowledge concerning fluid and electrolyte balance; liberal administration of whole blood when necessary; judicious preoperative regard for renal injury; early referral by the family physician for evaluation; and operation by the urologist before secondary complications develop from obstructive prostatism.

REFERENCES

1. Gailbraith: Cited by Davis, D. M.[2]
2. Davis, D. M.: Notes on prostatic surgery, and the results which should be expected of it. J. Urol. 69:539-544, 1953.
3. Rowe, R. B. and Kimbrough, J. C.: A study of incontinence and impotence following prostatic surgery. Mil. Surgeon 108:481-484, 1951.
4. Longley, J. R. and Cook, E. N.: Mortality and morbidity after transurethral resection in cases of Parkinson's syndrome. Proc. Staff Meet., Mayo Clin. 26:264-266, 1951.
5. Creevy, C. D.: The mortality of transurethral prostatic resection. J. Urol. 65:876-883, 1951.
6. Nesbit: Cited by Creevy, C. D.[5]
7. Moore, T. D.: Retropubic prostatectomy: Results and complications. J. Urol. 65:865-873, 1951.
8. Young, H. H. and Davis, D. M.: Young's Practice of Urology. Philadelphia, W. B. Saunders Company, 1926, vol. 1.

GENERAL PRACTICE REVIEW

Antibiotics: Use Versus Abuse

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BECAUSE of their ready availability, their remarkably low toxicity, and their promotion by aggressive advertising campaigns, antibiotics are currently being administered to an ever-increasing proportion of the population for a variety of reasons, many of which are unjustified. Antibiotic treatment as here alluded to is intended to include anything from prolonged therapy in hospitalized cases to the casual injection of penicillin or the dose of ACHROMYCIN® given to the ambulatory patient in the clinic or office. One report,[1] cited here as a striking example of this trend toward the indiscriminate use of antibiotics, states that in a certain general hospital approximately two-thirds of all the patients admitted during a single month, excluding obstetric patients and newborn infants, received antibiotics, either singly or in combination. The vast majority of these patients were treated with antibiotics in the absence of recognized infection, and such prophylactic therapy was applied especially frequently in surgical cases.

Although reduced incidence and morbidity of many infectious diseases have, of course, followed the introduction of antibiotics, these benefits have been offset with increasing frequency by undesirable side effects. These are of varying importance to the patient and include allergic reactions, the emergence of resistant strains of bacteria, specific syndromes caused by resistant replacement flora, and the masking of continuing or unrecognized infection by inadequate treatment administered before an etiologic diagnosis is established. It follows that the frequency of such complications could be reduced materially by exercising a more critical attitude toward assessing the indications for antibiotic administration. Keeping in mind the exigencies of a busy general practice for which laboratory facilities may not always be readily available, there are still a number of specific facts and general clinical concepts which are useful in deciding

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(1) when antibiotics are indicated and, if so, which to administer, and (2) when antibiotics are *not* indicated.

Allergic Reactions

The common complications and undesirable side effects will be considered only briefly, since they have been dealt with extensively in the literature.[2] Of the available antibiotics, penicillin, although virtually nontoxic, is the most frequent cause of allergic reactions. These allergic manifestations, occurring in about 10 per cent of all patients given penicillin, vary from mild transient skin eruptions and slight fever, through the serum sickness type of sensitivity reaction to immediate anaphylactic shock from which a number of fatalities have occurred.[3-5] A history of previous sensitivity, however well documented, may not preclude the later administration of penicillin, since such sensitivity may subside over a period of time and not reappear on subsequent administration of the drug. Either an intradermal or a scratch skin test should be performed on patients with histories of penicillin allergy, since those giving an unequivocal wheal and erythema reaction are more likely to show allergic manifestations with therapeutic doses than are patients with negative skin tests. In most of the reported cases of acute severe nonfatal anaphylactic reactions to penicillin, a subsequent skin test has produced a wheal and erythema reaction. Passive transfer of the specific skin sensitivity has been reported.[4] When penicillin sensitivity is suspected in a given case, even if the skin test is negative the antibiotic still should be administered in small amounts at first, with the usual precautions at hand for dealing with anaphylactic reactions. Full dosage can then be given if no untoward symptoms or signs are evident. Undesirable side effects from the newer broad spectrum antibiotics consist chiefly of gastrointestinal symptoms; allergic manifestations are unusual.

Resistant Bacterial Strains

The problem of the emergence of resistant strains of bacteria should be considered from several aspects. A change in the degree of resistance of the causative organism during treatment is not often of importance in the acute infections, except for those of the urinary tract due to the gram-negative bacteria. Although one strain of *Streptococcus viridans* isolated from a case of subacute bacterial endocarditis is reported to have increased in resistance to penicillin during therapy,[6] opportunities to detect such phenomena are rare, since treatment is usually designed to eradicate the causative organism by maintaining blood levels of antibiotic far exceeding those to which it can be shown initially to be sensitive by in vitro tests. Indeed, there is direct evidence that the susceptibility of greening streptococci to penicillin has not changed in the general population.[7] Beta hemolytic streptococci are still uniformly sensitive to penicillin, and only one resistant strain has been reported.[6] Likewise the meningococcus and the pneumococcus are still very susceptible to low concentrations of penicillin, and only one strain of type 1 pneumococcus has been encountered which was thought to be resistant.[6]

A more critical problem is the overgrowth, during treatment with an antibiotic to which they are not sensitive, of bacteria ordinarily constituting part of the normal flora of the respiratory or gastrointestinal tract, and not usually causative of acute disease.[8] Good examples of this phenomenon are the appearance of moniliasis during antibiotic therapy, and the development of pneumonia due to gram-negative organisms during prolonged penicillin therapy.[9, 10] Of growing concern has been the occurrence of staphylococcal enteritis following oral therapy with broad spectrum antibiotics and occasionally following oral penicillin or streptomycin. In these cases, hemolytic *Staphylococcus aureus* has appeared as the predominant or even sole organism in the bowel, with normal flora suppressed or eliminated.[11] The incidence of this potentially serious complication of antibiotic therapy is related to the occurrence of strains of *Staph. aureus*, an increasing percentage of which are resistant to penicillin as well as to other antibiotics.[12-19] The high incidence of carriers of such resistant strains in hospital personnel reported in several studies represents a real

and growing problem, especially in managing postoperative infections. In accordance with experience elsewhere, strains of *Staph. aureus* isolated at the Presbyterian Hospital from both outpatients and hospitalized patients during the period 1950 to 1954 included an increasing percentage resistant to penicillin. The percentage of strains resistant to penicillin was higher among those isolated from hospitalized patients than among those recovered from clinic or outpatients (figure 1).

Masking Infections

A special area in which the haphazard administration of penicillin or other antibiotics may have serious consequences is in undiagnosed subacute bacterial endocarditis. The insidious onset of this disease, often with no symptoms other than a little intermittent fever, fatigue and weight loss, is well known. Yet many patients will be admitted to the hospital because such vague symptoms have persisted despite the administration of a little penicillin, and these patients will be found to have a rheumatic background, indisputable evidence of valvular disease, and even petechiae, so that the diagnosis of subacute bacterial endocarditis becomes established virtually on clinical grounds alone. However, the advantage of isolating the responsible organism from the blood will have been forfeited by the prior antibiotic therapy inadequate to achieve a cure.

The importance of recovering the causative organism in suspected subacute bacterial endocarditis is obvious, since the determination of its in vitro sensitivity to antibiotics is a valuable guide in deciding the type, amount and extent of therapy. Although the majority of cases, when proved, are due to *Str. viridans*, a fair percentage are caused by nonhemolytic streptococci, frequently of Lancefield group D. The latter are often resistant to high concentrations of penicillin in vitro and are therefore more refractory from the clinical standpoint. Of 62 strains of *Str. viridans* isolated by blood culture from cases of subacute bacterial endocarditis at the Presbyterian Hospital between 1946 and 1954, 59 strains, or 95 per cent, were relatively sensitive to penicillin, 1 unit of penicillin or less per milliliter being bactericidal in vitro. Of 28 strains of nonhemolytic streptococci, 15 strains, or 54 per cent, showed the same order of sensitivity to penicillin, and the remainder were very resistant in vitro. In some cases, the organisms isolated could be shown to be less resistant in vitro to the combination of pencillin and streptomycin than to either antibiotic alone. This synergistic action of penicillin with streptomycin, especially on the enterococci, has been amply demonstrated both experimentally and clinically. In short, it is safe to say that in subacute bacterial endocarditis, almost more than in any other serious infection, the isolation and characterization of the causative organism are of prime importance with respect to the diagnosis, management and prognosis in the individual case.

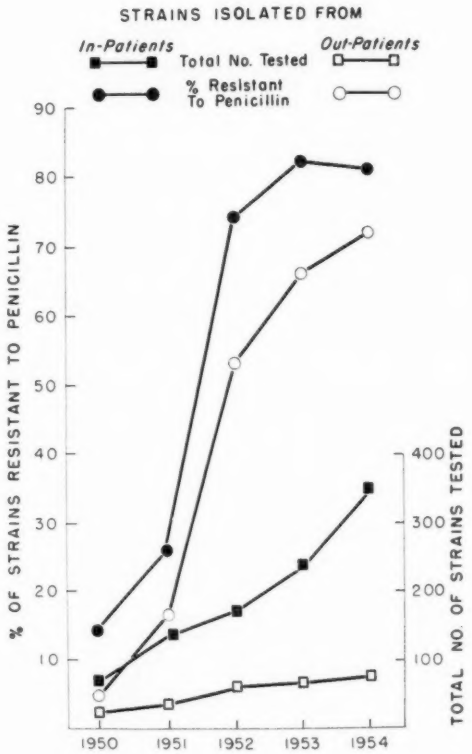

FIGURE 1. The increasing prevalence of penicillin-resistant *Staphylococcus aureus* as reflected in the changing in vitro sensitivity of strains isolated from 1950 through 1954.

TABLE 1

CLINICAL FEATURES OF THE COMMONER RESPIRATORY DISEASE SYNDROMES

DISEASE	ETIOLOGY	CLINICAL FEATURES			
		Onset	*Fever*	*Coryza*	*Other Signs and Symptoms*
Common cold	Viral	Abrupt	None (in adults)	Regularly	Malaise
Exudative tonsillitis and pharyngitis	Beta hemolytic streptococci, usually group A	Abrupt	Moderate	None	Cervical nodes, nasal congestion
	Infectious mononucleosis (possibly of viral etiology)	Variable	Moderate	None	Lymphadenopathy, splenomegaly
Pharyngoconjunctival fever	Adenoidal-pharyngeal-conjunctival agents (APC viruses; at least six immunologic types with common group-specific complement fixing antigen(s); types 3 and 4 (RI-67) probably most often implicated)	Gradual	Moderate	Occasionally	Lymphadenopathy, conjunctivitis in type 3 cases
Acute respiratory disease (ARD)		Gradual	Moderate	Frequently	Hoarseness, dry cough
Atypical pneumonia		Gradual	Moderate to high	Unusual	Severe headache, dry paroxysmal cough
	Rickettsia burneti; lymphogranuloma venereum, psittacosis-ornithosis group of larger viruses	Abrupt	Moderate to high	Unusual	
Primary atypical pneumonia	Probably viral; identity of agent(s) uncertain	Gradual	Moderate to high	Unusual	
Lobar pneumonia	Usually pneumococcus	Abrupt	High	May be preceded by a cold	Chest pain, chills, productive cough
Influenza	Viral (types A, A′, B, C, etc.)	Abrupt	Moderate	None	Constitutional; headache, dry cough

Meningitis is another category of acute infection in which the diagnosis may be masked by subcurative antibiotic treatment in the early stages. A patient with increasing signs of meningitis may be sent to the hospital after having received one injection of penicillin beforehand. Yet this small amount of penicillin will make it difficult or impossible subsequently to recover meningococci or pneumococci by culture of the spinal fluid or blood. However, the spinal fluid will still show a marked polymorphonuclear leukocytic reaction, which in itself constitutes strong evidence for the bacterial etiology of meningitis. It is therefore of the greatest importance to establish a specific diagnosis in patients with meningitis prior to the institution of antibiotic therapy whenever possible, since on such information will depend the correct management of individual cases.

It might be pointed out that in acute meningeal infections of bacterial etiology, with

TABLE 1

CLINICAL FEATURES OF THE COMMONER RESPIRATORY DISEASE SYNDROMES

Evidence of pulmonary involvement	LEUKOCYTE COUNT	DIFFERENTIAL LABORATORY TESTS	ANTIBIOTIC INDICATED	REMARKS
None	Normal total and differential	None	None	Antibiotics only for purulent sequelae
None	Elevated total and percentage of polymorphonuclear neutrophils	Isolation of streptococci, rise in antistreptolysin titer	Penicillin, (Aureomycin, Terramycin)	Antibiotics for preventing rheumatic fever, acute glomerulonephritis
None	Low to high total, high percentage of lymphocytes	Abnormal monocytes, rise in heterophil antibody titer	None	Prolonged clinical course
None	Normal total and differential	Rise in titer of complement fixing antibodies to group-specific antigen(s), no rise in cold or streptococcus MG agglutinin titers	None	May resemble common cold except for fever, and streptococcal sore throat except for absence of leukocytosis
Tracheobronchitis, no x-ray changes	Normal total and differential		None	
Scattered rales, soft nodular or patchy nonlobar x-ray shadows more extensive than physical signs, migratory pneumonitis with new areas of infiltration during acute disease	Polymorphonuclear leukocytosis late in course, occasionally with spread of pulmonary lesions		None	Treatment symptomatic (e.g., APC® capsules)
		Rise in specific complement fixing antibody titer, no rise in cold or streptococcus MG agglutinin titers	Aureomycin, Terramycin	
		Rise in cold and/or streptococcus MG agglutinin titer	Aureomycin (?), Terramycin (?)	Value of antibiotics still debatable
Lobar consolidation by physical and x-ray examination	Polymorphonuclear leukocytosis	Isolation of pneumococcus or other respiratory pathogen	Penicillin (broad spectrum antibiotics)	Sharp clinical response virtually diagnostic
Fine rales, rarely x-ray shadows	Normal total and differential	Rise in complement fixing antibody and antihemagglutinin titers	None	

the exception of leptospiral meningitis, the blood leukocyte count is elevated as a rule, with polymorphonuclear leukocyte predominance, whereas in infections of viral etiology the total white blood cell count is usually normal, with a normal or lymphocytic differential. In the common viral or so-called aseptic meningitides, which include lymphocytic choriomeningitis, mumps, herpes simplex and poliomyelitis, the spinal fluid, of course, also shows a lymphocytic reaction.

Indications and Contraindications

With the significant complications of antibiotic therapy in the background, the physician nonetheless is repeatedly tempted to use antibiotics, whether or not clear-cut indications or contraindications are present. Indeed, it frequently takes more fortitude on his part to withhold such treatment than to administer it when the clinical picture is not well defined and when patient and relatives are pressing for action and results. One of the salient facts

which still holds true is that none of the common viral diseases are susceptible to antibiotic treatment, with a few exceptions to be considered later. This is in contrast to most, if not all, of the common bacterial diseases, which can be treated successfully provided the correct etiologic diagnosis is made. How is one to make this very important distinction without the extensive facilities for bacteriologic and serologic investigation? A few specific examples may help to indicate that presumptive differentiation between viral and bacterial disease can be made primarily on the basis of accurate clinical observations, with the help of one or two simple laboratory procedures that can be carried out easily in the home or office.

The single category of illness for which antibiotics are administered most frequently, and in many cases without sufficient indication, is that of the acute respiratory disease syndromes. Nonetheless, a distinction between probable bacterial and viral etiology frequently can be made with sufficient certainty to justify either administering or withholding antibiotics. In table 1, clinical features of the commoner respiratory disease syndromes are listed. Differential laboratory tests, presented for reference, are not always necessary in order to arrive at a justifiable decision as to whether or not to use antibiotics.

The viral etiology of the common cold is well established on both experimental and epidemiologic grounds, although the virus itself has not been isolated with sufficient ease or regularity to allow more precise characterization. The common cold, however severe, is rarely accompanied by fever or leukocytosis unless some secondary bacterial complication arises. Such complications, including otitis media, acute sinusitis and mastoiditis, are the sole justification for antibiotic therapy in managing the common cold.

Exudative pharyngitis, with cervical lymphadenopathy and tonsillitis, is often caused by beta hemolytic streptococci, usually Lancefield group A, although other groups have been implicated.[20] Leukocytosis is the rule, with polymorphonuclear leukocytic predominance. The presence of group A streptococci in the throat is an important indication for the prompt administration of penicillin in moderate dosage over a length of time sufficient to insure eradication of the organisms. In situations where bacteriologic studies are not feasible, exudative pharyngitis or tonsillitis should nevertheless be treated with antibiotics in order to eliminate group A streptococci in case they are present. There is good evidence that at least a week or 10 days of antibiotic administration is necessary to eradicate the organisms. In addition to limiting the possible spread of streptococci to family contacts, antibiotic administration is an effective prophylactic measure against the nonsuppurative sequelae of acute streptococcal infections, namely, rheumatic fever and acute glomerulonephritis.[21,22] A number of studies have shown that a long-acting penicillin preparation is effective, since low but still detectable levels of penicillin are maintained for 12 to 14 days after a single injection of 600,000 units.[23-25] Broad spectrum antibiotics have also been used successfully but are probably less reliable than penicillin for this purpose.[26-28]

Infectious mononucleosis has been included in the table, since its onset, with acute pharyngitis, tonsillitis and lymphadenopathy, is often very similar to that of streptococcal infection and can be differentiated with certainty only later in the course of the disease by the lymphocytic response in the blood, the appearance of abnormal mononuclear cells and a rise in the heterophil antibody titer. In addition, the spleen is usually palpable.

Less clearly defined from the clinician's viewpoint are the other viral respiratory disease syndromes, and in turn the indications, if any, for antibiotic therapy. The discovery of a new class of respiratory disease agents[29-31] has provided an etiologic explanation for some of these syndromes. This group of viruses, comprising at least six immunologic types, is designated as the "adenoidal-pharyngeal-conjunctival" (APC) group of agents. They can cause exudative pharyngitis, with or without coryza, which may be indistinguishable from the common cold except for fever, and may resemble streptococcal sore throat except for the absence of leukocytosis. Conjunctivitis,

frequently unilateral, seems to be a constant feature of infection with type 3 APC virus.[32] Group-specific complement fixation tests, not yet generally available, have served to identify the APC viruses as the cause of widespread respiratory disease both in the civilian population and in military recruits, accounting for a large proportion of cases previously designated as undifferentiated acute respiratory disease.[33] These cases show nothing particularly distinctive except for a fairly uniform pattern of moderate fever, hoarseness and fine, scattered rales without x-ray evidence of pulmonary infiltration.

At least one member of the APC group of viruses (type 4, corresponding to the RI-67 agent described by Hilleman and Werner[29]) is responsible for some cases of so-called atypical pneumonia. The clinical features are similar to those of the disease entity originally designated as "primary atypical pneumonia, etiology unknown,"[34-36] which consist of paroxysmal, nonproductive cough, variable physical signs in the chest, and x-ray lesions the extent of which frequently exceeds that of the physical signs. As seen by x-ray, the lesions consist usually of patchy areas of consolidation, on rare occasions in lobar distribution. Evidence of pulmonary infiltration may persist for some time after defervescence and fairly complete clinical recovery. In addition to their distinction on the basis of specific complement fixation tests, infections due to the APC group are characterized by the absence, during convalescence, of cold agglutinins and agglutinins for streptococcus MG. Cold and streptococcus MG agglutinins, however, are fairly constant features in cases of primary atypical pneumonia caused by an agent or agents as yet unidentified but unrelated to the APC group.

The clinical picture of atypical pneumonia is also seen in Q fever, caused by *Rickettsia burneti*, and in infections with the lymphogranuloma venereum and psittacosis-ornithosis group of larger viruses. Cold agglutinins do not appear in either of these last two infections, which, however, can be diagnosed during convalescence by a rise in specific complement fixing antibodies to the antigens of the respective organisms. As to antibiotic therapy in the atypical pneumonia syndrome, none has been found to be effective in the cases caused by the APC group of viruses. Primary atypical pneumonia, with cold and/or streptococcus MG agglutinins, has been held to respond to AUREOMYCIN® and TERRAMYCIN®.[37-42] This particular question has not been conclusively settled,[43] although the evidence favors using the broad spectrum antibiotics. Both Q fever and psittacosis-ornithosis are known to respond well to Aureomycin or Terramycin. Since the fact that the various etiologies of the atypical pneumonia syndrome can be established only on the basis of special serologic reactions, and because some responsible agents seem to be susceptible to antibiotics, it would seem quite logical to use Terramycin or Aureomycin in treating the more severe cases with clinical and x-ray evidence of pneumonitis but with normal leukocyte count and nonproductive cough. Penicillin is ineffective and should not be used except when sequelae due to secondary bacterial infection arise.[44]

The atypical viral pneumonias should be distinguished clinically from the acute bacterial pneumonias, chiefly the pneumococcal type. This can be accomplished with fair certainty without elaborate laboratory aids. The abrupt onset, usually high fever, regularly productive cough with purulent or blood-tinged sputum, and marked leukocytosis, are strong evidence for a bacterial etiology. A prompt response to penicillin, the drug of choice for pneumococcal pneumonia, virtually establishes this diagnosis. Broad spectrum antibiotics are also effective.[45-47] It might be pointed out that despite the reduction in mortality accomplished by antibiotic therapy, pneumococcal pneumonia still has an appreciable fatality rate, and certain factors, such as age, unusual leukopenia, concomitant unrelated disease and infection due to types 1 and 3 are significant.[48]

Influenza, a diagnosis applicable strictly to the disease caused by several immunologically distinct types of virus, shows certain features which distinguish it from the foregoing clinical entities. The onset may be abrupt and the fever moderate. Symptoms are primarily con-

stitutional without any striking localizing signs. Pulmonary lesions, by either physical signs or x-ray, are rare except in large epidemics. As with the other respiratory diseases of viral etiology, the leukocyte count is usually normal. A specific retrospective diagnosis can be made by a rise in complement fixing antibodies and antihemagglutinins. Influenza does not respond to any antibiotic.

In vitro antibiotic sensitivity tests were performed by Miss Louise Goode in the Department of Microbiology, Columbia University College of Physicians and Surgeons, New York, New York.

REFERENCES

1. Wei-Ping Loh and Street, R. B.: Study of the use of antimicrobial agents in a community hospital. New England J. Med. 251:659, 1954.
2. Finland, M. and Weinstein, L.: Complications induced by antimicrobial agents. New England J. Med. 248:220, 1953.
3. Higgins, G. A. and Rothchild, T. P. E.: Fatal anaphylactic shock from procaine penicillin. New England J. Med. 247:644, 1952.
4. Mayer, P. S., Mosko, M. M., Schutz, P. J., Osterman, F. A., Steen, L. H. and Baker, L. A.: Penicillin anaphylaxis. J.A.M.A. 151:351, 1953.
5. Feinberg, S. M., Feinberg, A. R. and Moran, C. F.: Penicillin anaphylaxis, nonfatal and fatal reactions. J.A.M.A. 152:114, 1953.
6. Hirsh, H. L., Dowling, H. F. and Robinson, J. A.: Organisms resistant to penicillin obtained from patients. Arch. Int. Med. 82:310, 1948.
7. Berntsen, C. A.: Unaltered penicillin susceptibility of streptococci. Study of alpha hemolytic streptococci causing endocarditis, 1944 to 1954. J.A.M.A. 157:331, 1955.
8. Keefer, C. S. (Editorial): Alterations in normal bacterial flora of man and secondary infections during antibiotic therapy. Am. J. Med. 6:665, 1951.
9. Sommer, L. S. and Favour, C. B.: Biological complications of penicillin therapy. Am. J. Med. 7:511, 1949.
10. Weinstein, L., Goldfield, M. and Te-Wen Chang: Infections occurring during chemotherapy. New England J. Med. 251:247, 1954.
11. Fairlie, C. W. and Kendall, R. E.: Fatal staphylococcus enteritis following penicillin and streptomycin therapy. J.A.M.A. 153:90, 1953.
12. Dowling, H. F., Lepper, M. H. and Jackson, G. G.: Clinical significance of antibiotic-resistant bacteria. J.A.M.A. 157:327, 1955.
13. Needham, G. M. and Nichols, D. R.: Recent changes in sensitivity of *Micrococcus pyogenes* to various antibiotic agents. J. Lab. & Clin. Med. 41:150, 1953.
14. Bondi, A., Pfaff, F., Free, E. and Swerlick, R.: Public health aspects of the development of antibiotic-resistant staphylococci. Am. J. Pub. Health 44:789, 1954.
15. Howe, C. W.: Postoperative wound infections due to *Staphylococcus aureus*. New England J. Med. 251:411, 1954.
16. Metzger, J. F., Fusillo, M. H., Roerig, R. N. and Ernst, K. F.: Phage typing of antibiotic-resistant staphylococci. III. Infection, crossinfection and superinfection. New England J. Med. 250:1030, 1954.
17. Lepper, M. H., Dowling, H. F., Jackson, G. G. and Hirsch, M. M.: Epidemiology of penicillin- and aureomycin-resistant staphylococci in a hospital population. Arch. Int. Med. 92:40, 1953.
18. Editorial: Micrococcus pseudomembranous enterocolitis, a complication of antibiotic therapy. J.A.M.A. 157:346 (January 22) 1955.
19. Editorial: Spread of antibiotic-resistant staphylococci. New England J. Med. 249:711, 1953.
20. Commission on Acute Respiratory Diseases: The rôle of Lancefield groups of beta-hemolytic streptococci in respiratory infections. New England J. Med. 236:157, 1947.
21. Massell, B. F., Sturgis, G. P., Knobloch, J. D., Streeper, R. B., Hall, T. N. and Norcross, P.: Prevention of rheumatic fever by prompt penicillin therapy of hemolytic streptococcic respiratory infections. J.A.M.A. 146:1469, 1951.
22. Rammelkamp, C. H., Wannamaker, L. W. and Denny, F. W.: The epidemiology and prevention of rheumatic fever. Bull. New York Acad. Med. 28:321, 1952.
23. Breese, B. B.: Treatment of beta hemolytic streptococcic infections in the home. J.A.M.A. 152:10, 1953.
24. Stollerman, G. H. and Rusoff, J. H.: Prophylaxis against group A streptococcal infections in rheumatic fever patients. J.A.M.A. 150:1571, 1952.
25. Wannamaker, L. W., Denny, F. W., Perry, W. D., Rammelkamp, C. H., Eckhardt, G. C., Houser, H. B. and Hahn, E. O.: The effect of penicillin prophylaxis on streptococcal disease rates and the carrier state. New England J. Med. 249:1, 1953.
26. Breese, B. B.: Aureomycin in the treatment of beta hemolytic streptococcal infections. J. Pediat. 40:85, 1952.
27. McVay, L. V. and Spruit, D. H.: Aureomycin in the prophylaxis of rheumatic fever. New England J. Med. 249:387, 1953.
28. Denny, F. W., Wannamaker, L. W. and Hahn, E. O.: Comparative effects of penicillin, aureomycin, and terramycin on streptococcal tonsillitis and pharyngitis. Pediatrics 11:7, 1953.
29. Hilleman, M. R. and Werner, J. H.: Recovery of a new agent from patients with acute respiratory illness. Proc. Soc. Exper. Biol. & Med. 85:183, 1954.
30. Huebner, R. J., Rowe, W. P., Ward, T. G., Parrott, R. H. and Bell, J. A.: Adenoidal-pharyngeal-conjunctival agents. A newly recognized group of common viruses of the respiratory system. New England J. Med. 251:1077, 1954.
31. Parrott, R. H., Rowe, W. P., Huebner, R. J., Bernton, H. W. and McCullough, N. B.: Outbreak of febrile pharyngitis and conjunctivitis associated with type 3 adenoidal-pharyngeal-conjunctival virus infection. New England J. Med. 251:1087, 1954.
32. Bell, J. A., Rowe, W. P., Engler, J. I., Parrott, R. H. and Huebner, R. J.: Pharyngoconjunctival fever. Epidemiological studies of a recently recognized disease entity. J.A.M.A. 157:1083, 1955.
33. Commission on Acute Respiratory Diseases: Clinical patterns of undifferentiated and other acute respiratory diseases in army recruits. Medicine 26:441, 1947.
34. Longcope, W. T.: Bronchopneumonia of unknown etiology. Bull. Johns Hopkins Hosp. 47:268, 1940.
35. Kneeland, Y. and Smetana, H. F.: Current bronchopneumonia of unusual character and undetermined etiology. Bull. Johns Hopkins Hosp. 40:229, 1940.
36. Official Statement: Primary atypical pneumonia, etiology unknown. War Med. 2:330, 1942.
37. Finland, M., Collins, H. W. and Wells, E. B.: Aureomycin in the treatment of primary atypical pneumonia. New England J. Med. 240:241, 1949.
38. Meiklejohn, G. and Shragg, R. I.: Aureomycin in primary atypical pneumonia. J.A.M.A. 140:391, 1949.
39. Melcher, G. W., Gibson, C. D., Rose, H. M. and Kneeland, Y.: Terramycin in the treatment of pneumococcic and primary atypical pneumonia. J.A.M.A. 143:1303, 1950.
40. Schoenbach, E. B. and Bryer, M. S.: Treatment of primary atypical nonbacterial pneumonia with aureomycin. J.A.M.A. 139:275, 1949.
41. Kneeland, Y., Rose, H. M. and Gibson, C. D.: Aureomycin in the treatment of primary atypical pneumonia. Am. J. Med. 6:41, 1949.
42. Collins, H. S., Wells, E. B., Gocke, T. M. and Finland, M.: Treatment of primary atypical pneumonia with aureomycin. Am. J. Med. 8:4, 1950.
43. Walker, S. H.: Ineffectiveness of aureomycin in primary atypical pneumonia. Am. J. Med. 15:593, 1953.
44. Jones, P. N., Bigham, R. S. and Manning, P. R.: Use of antibiotics in nonbacterial respiratory infections. J.A.M.A. 153:262, 1953.
45. Collins, H. S., Gocke, T. M. and Finland, M.: Aureomycin therapy of nonpneumococcic and nontuberculous bacterial pulmonary infections. Arch. Int. Med. 81:875, 1949.
46. Gibson, C. D., Nushan, H. and Anderson, D. N.: The treatment of bacterial pneumonia with erythromycin: a controlled clinical study. Ann. Int. Med. 41:112, 1954.
47. Frei, E., Auner, C. R., Van Metre, T. E. and Zubrod, C. G.: A comparison of the efficacy of tetracycline and penicillin in the treatment of pneumococcal pneumonia. New England J. Med. 252:173, 1955.
48. Van Metre, T. E.: Pneumococcal pneumonia treated with antibiotics. The prognostic significance of certain clinical findings. New England J. Med. 251:1048, 1954.

CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Report of Case

A 50 year old shoemaker was admitted to the Neurosurgical Service in September 1953 with a diagnosis of possible prolapsed nucleus pulposus.

His past history included the usual childhood diseases. In 1915, at the age of 19 years, he fell out of a tree and injured his dorsal spine. He had a moderate amount of pain and remained in bed for a year. A cast was not applied and he did not have medical treatment. There was no paralysis or any loss of sensation.

He had a tonsillectomy in 1924. There was no history of venereal disease. In 1943 he was told that he had high blood pressure.

His father died of "old age," his mother of "female trouble"; their ages at death were not given. Two brothers and two sisters were living and well. One brother died from "stomach trouble" and one from high blood pressure. A sister died following an abdominal operation.

The patient served in the United States Army as an infantryman from June 1917 to May 1918. He was given a medical discharge with a diagnosis of arthritis of the left knee.

He stated that he smoked about six cigarettes a day and did not use alcohol or drugs. In addition to working as a shoemaker during the day, he worked as a watchmaker at night. In the latter job he was exposed to minimal amounts of benzol and carbon tetrachloride.

Ever since his accident in 1915, he had had trouble with pain in the back. This had taken the form of infrequent episodes of moderately severe pain starting in the dorsal spine and radiating around the right flank to the right lower quadrant. The attacks sometimes occurred once a year and sometimes once in five years. They usually lasted about a week. They often had been diagnosed as appendicitis, but the appendix had not been removed.

In October 1945 the patient decided he was overweight at 207 lb. and reduced to 170 lb. in a few months by discontinuing his evening meal.

About January 1953 he first noticed that his back and legs ached slightly after a day's work. The pain was not severe and was relieved by an hour's rest. It never interfered with his sleep. About May 1, 1953 the patient had an episode of back pain which he said was identical with his previous attacks. As usual, the pain became less after a week and finally disappeared. However, with disappearance of the upper back pain, he noticed moderately severe pain in the lower lumbar region. It was sharp and radiated down both

legs, anteriorly and posteriorly, but was much more severe in the left leg. Sudden motion, lifting, coughing or sneezing did not aggravate the pain, and it sometimes was relieved by taking ordinary analgesics. Gradually the pain became more severe, until at the time of admission the patient said it was hard for him to walk.

About two months prior to admission he first noticed numbness and tingling over the dorsum of the left foot and lateral aspect of the left calf. He thought, however, that this had improved somewhat during the month before admission. Also during the two months before admission, he had had attacks of pain in the right upper quadrant of the abdomen when his back pain was particularly severe. He described this as a feeling of gas in the abdomen which was worse after eating and relieved by taking analgesics. He had not used alkalies. There was no nausea, vomiting, hematemesis, constipation, belching or flatus. He had noticed some anorexia, and said his bowel habits had changed from a usual one stool a day to about three a day. The legs were not weak. The patient thought he had lost 20 lb. in the 60 days before admission.

Inventory by systems did not elicit further significant information except some "kidney trouble" and an infection which had cleared following medical treatment, about a year previously. He had a work-up at another hospital the previous summer. A definite diagnosis had not been made, but surgery for herniated nucleus pulposus was considered. The patient refused this.

Physical examination revealed a well-developed, well-nourished man who did not appear acutely ill. He limped slightly, favoring the left leg. Blood pressure was 146/78. His head, neck, heart and lungs were normal. The liver was palpable at the costal margin on deep inspiration and was soft, smooth and quite tender. A kyphosis was maximal at about the first lumbar vertebra. The spine was not rigid and there was no scoliosis. The lower sacral area was slightly tender, but the pain did not radiate down the legs. There was moderate spasm of the erector spinae muscles bilaterally. The patient could touch the floor with the knees held straight. Romberg's sign was negative. Straight leg raising was limited to 85 degrees bilaterally. Naffziger's and Lasègue's signs were negative. All deep and superficial reflexes were normal except the abdominal reflexes, which were absent. There were no pathologic reflexes.

On September 25, 1953, at about midnight, the patient experienced sudden pain at the middle third of the volar aspect of the right forearm, with reddish discoloration and tenderness to pressure. A rolling, tender, palpable, cordlike mass was felt in this area and was believed to be a thrombosed vessel. A diagnosis of thrombophlebitis was made and he was transferred to the Peripheral Vascular Service for treatment on September 26. Penicillin, DICUMAROL® and heparin were administered, and by October 4 the arm tenderness had improved. The patient continued to complain of severe backache, for which codeine was necessary. On October 7 pain was felt in the left calf, and Homans' sign was positive. This improved slowly. On October 21 the liver was enlarged three fingerbreadths below the right costal margin and was tender. The tenderness over the calf was absent at this time, and Homans' sign was "almost negative." The patient was on Dicumarol during this period. On October 25 tenderness was noted in the right popliteal space. Homans' sign was positive on the right, and pain and tenderness appeared over the Achilles tendon. His leg pains improved slowly but his backache was severe.

On October 31, examination showed the liver five fingerbreadths below the right costal margin, and one examiner thought the spleen was palpable at the left costal margin. On November 2 the patient complained of mild diarrhea. On November 4 a medical consultant saw the patient and noted that the skin had a subicteric tint but the sclerae were not discolored. Blood pressure was 150/24, and soft, nontransmitted systolic murmurs were detected over the apex and base. The liver was palpable, firm and smooth and extended approximately to the level of the umbilicus. This examiner could not definitely make out the spleen. Pedal pulses were adequate, but there was thickening and tortuosity of all the palpa-

ble arteries. An area of redness, swelling and tenderness was seen on the dorsum of the right foot. Knee jerks were quite active. Considerable additional work-up was ordered, including biopsy of vein and muscle.

Because of the migratory thrombophlebitis, severe pain in the back and legs, and increasing size of the liver, the patient was transferred on November 10 to the Medical Service. On November 14, 1 cc. of PITRESSIN® was administered in connection with x-ray study of the gallbladder. Within an hour after the films were made, the patient complained of precordial pain with radiation down the left arm. Examination within an hour of the onset of this pain showed paresis of the left arm, left leg, left half of the face (not including the forehead) and left side of the tongue. An emergency electrocardiogram taken at this time revealed changes consistent with an acute anterior myocardial infarction. (An electrocardiogram on November 8 was reported as "probably within normal limits.") Blood pressure was 120/78. The temperature, which prior to November 14 had not exceeded 99.6° F., reached 102° F. on that day and ranged from normal to 105° F. thereafter.

The patient did not void on November 14 and was catheterized. Subsequently, catheterization was required until the time of his death. On November 17, fine moist rales were noted in the left lower chest, with decreased resonance in this area. On November 19, purpuric areas appeared on the tip of the nose and on the left cheek. The next day these were larger. There was little improvement in the hemiplegia. Examination of the eyegrounds did not show hemorrhage, papilledema or significant arterial or venous spasm. Respirations were intermittent; pulse was 102 and regular. On November 21 two new purpuric areas appeared on the left cheek and one on the left ear. Gangrene did not develop in these areas. The left dorsalis pedis and posterior tibial arteries were not palpable, although the popliteal was normal. The right radial and ulnar arteries were not palpable, but the brachial was good in the antecubital fossa. Otherwise the arteries were normal. Blood pressure was 126/72. The patient died at 9:40 P.M. on November 21. No statement was made as to type of death.

Discussion by Medical Consultant

DR. DAVID ABRAMSON: The rapid increase in size of the liver during his hospital course is of interest. When the patient was first admitted, the liver was just palpable, and shortly before he died it was down to the level of the umbilicus. Signs of congestive heart failure were not present during this period, but there was some evidence of reduced liver function although the bilirubin content of the blood was not altered.

It appears that he had thrombosis of the superficial veins on the volar aspect of his right forearm and then the dorsum of his right foot and posterior surface of his left foot, with some involvement of the deep veins in both legs. There were no superficial signs of inflammation.

I already stressed the absence of pulsations. Also of interest was the development of a typical coronary infarction, probably brought about by the 1 cc. of Pitressin.

Heart murmurs were not heard initially, and subsequently a murmur was noted. Symptoms indicating heart failure were not present. The size of the heart was normal and there was no edema, signs of dyspnea or congestive trouble.

Of interest, too, is that despite the findings of the peripheral vessels, the eyegrounds were normal.

The left-sided hemiparesis occurred practically at the same time as did the myocardial infarct (an hour later), which cleared up to some extent.

For purposes of differential diagnosis, I shall discuss separately the involvement of the different organ systems. First, with regard to the attacks of superficial and deep thrombophlebitis, such findings can be associated with a number of noninfectious systemic conditions: (1) superficial idiopathic migratory thrombophlebitis; (2) superficial migratory thrombophlebitis associated with thromboarteritis obliterans; (3) malignancy of the visceral organs; (4) congestive heart failure; (5) other less frequent causes such as leu-

kemia, pernicious anemia and polycythemia.

The first obviously does not apply, since it explains only a part of the syndrome.

I believe there is some evidence to support the second possibility. Approximately 40 per cent of all patients with thromboarteritis obliterans have a history of superficial migratory thrombophlebitis early in the disease. Assuming the presence of thromboarteritis obliterans could also explain the findings in the heart and brain. This condition by no means limits itself to peripheral blood vessels. Also, bizarre types of cerebral accidents may occur in the course of thromboarteritis obliterans, and from this angle the clinical findings with regard to the brain condition readily fall into such a category. However, against the diagnosis are several factors. The first is his age—50. Rarely does thromboarteritis obliterans affect people in that age group. Generally they are from 20 to 40 years of age when it first begins. Secondly, it rarely produces lesions of the face, as were seen in this case, indicating obliteration of the blood vessels. It is rarely due to large vessels becoming obliterated as quickly as they did in this case—a matter of days. In my experience the shortest time has been four, five or six months.

Malignancy, particularly of abdominal viscera, is a good possibility. An increased coagulability of the blood was perhaps a result of toxic absorption from cancerous lesions or from prolonged bed rest and general cachexia, generally associated with such a condition. Thrombophlebitis of the superficial and deep veins in the anterior trunk may be one of the first clinical manifestations of obscure carcinoma, particularly in the pancreas or lungs. In fact, one should suspect visceral lesions in elderly individuals in whom thrombophlebitis of either small or large veins develops with a minimal periphlebitic reaction if no other symptom is present. Abdominal pain, anorexia, loss of weight and rapid enlargement of the liver in the absence of congestive heart failure support the diagnosis of carcinoma.

Thrombophlebitis may complicate a number of other noninfectious systemic diseases, chief among them being congestive heart disease associated with heart failure. It often occurs in the late stages of the disease, and it is possible that, in failure, the venous blood stream is slowed sufficiently to cause a condition favoring intravascular venous clotting.

Arterial thrombosis also may occur in the terminal stage of congestive heart failure. However, in the present case signs of congestive heart failure did not appear. Such conditions as myelogenous and lymphatic leukemia, pernicious anemia, and polycythemia also predispose to thrombophlebitis, but there is little evidence that they existed in this case.

One's ability to give plausible reasons for thrombophlebitis does not explain the rest of the clinical picture. Whenever so many bizarre happenings occur and one encounters difficulty in placing the findings in any known clinical syndrome or finds it necessary to assume that a number of unrelated conditions coexist in order to explain the various findings, one must consider the possibility of some type of generalized vasculitis. Periarteritis nodosa comes to mind first. This affects veins as well as arteries. Recent work has shown that periarteritis nodosa is a misnomer, since the pathologic state affects veins as well as arteries. Favoring periarteritis nodosa in the present case are a vague history of hypertension since 1943 (although not observed at the time of admission), a vague history of kidney trouble, presence of an eosinophilia up to 20, and lesions on the nose, cheeks and ears, simulating gangrene. I have seen a number of cases of proved periarteritis nodosa in which the patients had gangrenelike lesions at the periphery of the body, tips of the ears, nose and tips of the fingers. Other findings that would conform to the diagnosis of periarteritis nodosa are gastrointestinal complaints, coronary occlusion, and some type of cerebral artery spasm or occlusion.

Another possibility is associated with disseminated lupus erythematosus. Libman-Sacks' disease also must be considered. Disseminated lupus, like rheumatic fever, appears to be a diffuse disease, with the changes in the blood vessels affecting the wall rather than the endothelium. The characteristic changes are edema of subendothelial tissue and endothelial proliferation on the heart valves, and in some in-

stances the endothelium may desquamate. Deposits of platelets and fibrin will then form on the raw surface, producing vegetations, with acute or subacute bacterial endocarditis. This is the typical finding in Libman-Sacks' disease. The lumina of the peripheral vessels become narrowed or obliterated by the endothelial proliferation. Because of widespread involvement, the visible and the bizarre facial changes in this case may have been a typical manifestation of the butterfly lesion present in disseminated lupus, though they differed considerably from the characteristic change noted in this condition.

Another possibility with regard to the facial lesions is a ball thrombus in the left auricle. This may block circulation completely but transiently, and during such periods definite obstruction in the peripheral circulation and in the brain will be noted. Those at the periphery consist of absent pulses, cadaveric discoloration of fingers and toes, and similar lesions in the face. Invariably it is associated with mitral stenosis. This condition was not noted in this case.

The possibility that some of the findings were due to emboli arising from mural thrombi in the heart also must be considered. Against this, however, is the fact that the hemiparesis occurred approximately one hour after the onset of the acute myocardial infarction. It is improbable that a mural thrombus could develop in so short a time and be sufficiently large to account for the large number of emboli to different portions of the body. If the disappearance of the pulses in the extremities was due to embolization, certainly it was not associated with the characteristic findings that follow sudden occlusion of a large peripheral artery. Ordinarily, sudden occlusion of a large vessel in an extremity produces severe pain and paresis and a cadaveric appearance of the distal portion. The hand or foot becomes colder than its mate, and a stocking-glove type of anesthesia is elicited. None of these findings were observed, and hence the possibility that the disappearance of the pulses was due to embolization should be given little weight. However, had the patient lived long enough, some of the signs associated with a reduced arterial blood flow might have manifested themselves.

Idiopathic simple arterial thrombosis also must be considered. In this condition there is no history of an etiologic factor for thrombosis such as heart disease, blood dyscrasia or recent operations. The patient appears to be in good health, when, without cause, thrombosis of the peripheral arteries occurs, associated with thrombosis in veins and infarctions of lungs, kidneys, spleen, brain and myocardium. Generally there is an increased index of blood plasma coagulability or a high platelet count which may predispose toward thrombosis. Venous thrombosis may antedate arterial thrombosis, as is readily understandable, since the blood flow is so much slower in venous channels than in the arterial tree.

Ordinarily, occlusion of a large artery is ushered in by extensive gangrene of the distal portion of the extremity, or only the digits may be affected. At times the process does not progress to gangrene, but chronic arterial insufficiency may result and pathologic examination discloses the arterial lumen to be completely occluded by a homogenous thrombus containing relatively few fibroblasts. Secondary inflammatory reaction in the arterial walls is minimal, and degenerative changes are not present in the media of the vessel.

In the present case, findings may be considered to fall into this category except that rarely does idiopathic simple arterial thrombosis affect individuals in the fifth decade of life. In most instances the patient is young.

X-ray Examination

DR. WALTER J. DE NYSE: With regard to the chest x-rays, there is nothing unusual about the chest of this man. The heart is more the transverse type, which probably makes it look a little larger.

DR. WALLACE F. CHILDS: His knee is essentially normal, with a slight amount of decalcification but no evidence of arthritis. This examination was made two days before the patient died. The cardiac shadow is enlarged. The gallbladder examination was not successful, in that there is no visualization of the gallbladder. The film shows the old injury of

FIGURE 1. Massive infarction of left ventricular wall.

the spine, and the liver. A request was made to repeat this examination, but the patient died before we could do it.

PATHOLOGIST: If there are no further questions or comments, the postmortem findings will be given.

Postmortem Examination

Postmortem examination disclosed the body of a well-developed, well-nourished 50 year old white man. The body weighed about 190 lb. and measured 172 cm. in length.

The skin of the nose and left malar areas was markedly discolored. These lesions appeared closely to represent areas of thrombosis. The tissue was quite indurated, but the skin was not broken. Areas of discoloration also were noted on the left leg and thigh following the large veins. On palpation, there was some evidence of induration of the deep tissues. The skin, however, was not involved. No discolorations were noted of either arm or forearm.

Examination of the chest disclosed about 2000 cc. of brownish fluid on the left, and 300 cc. of straw-colored fluid on the right. The left lung was partially collapsed. Bilateral bronchopneumonia was noted at the bases,

FIGURE 2. Microscopic section showing recent infarction of left ventricular wall.

and an infarction, 5 cm. in diameter, at the left base posteriorly was hemorrhagic and showed evidence of central necrosis. On cut section, numerous grayish-white, circumscribed tumor nodules were found in all lobes,

the largest 3 cm. in diameter. Careful dissection disclosed no connection with the bronchial tree. The pericardial sac was enlarged to the left, and on opening the sac, a massive infarction could be seen involving the anterior portion of the left ventricle. The heart weighed 430 gm. Section of the heart disclosed a recent thrombosis of the anterior descending coronary artery, causing massive infarction of the entire anterior wall, involving the apex and a portion of the septum. The cut surface was grayish-red and showed early evidence of degeneration. There was no evidence of mural thrombus formation. The left ventricle wall measured 1.8 cm. in thickness. A large recent friable vegetation was noted on the aortic leaflet of the mitral valve. This was soft and easily dislodged. There was no gross evidence of injury of the endothelium. Sections of the peripheral vessels did not disclose evidence of injury or any specific inflammatory lesion.

Examination of the abdomen revealed a hard tumor mass 5 cm. in diameter involving the head of the pancreas. Small nodules were also noted in the body of the pancreas, numerous large nodules in the liver, and small nodules in the spleen. The nodules in the liver, kidneys and spleen were grayish-white and well demarcated and showed central umbilication. Microscopic examination of the tumor disclosed adenocarcinoma, sclerosing type, primarily in the pancreas. Section of the body of the pancreas disclosed some fibrous pancreatitis with fat necrosis, probably due to obstruction by the tumor mass.

Examination of bones of the spine did not disclose evidence of neoplasm.

Infarctions, hemorrhagic in type, were noted in the spleen and both kidneys.

The gastrointestinal tract did not show gross pathologic lesions.

The brain weighed 1300 gm. and showed a mild edema of the meninges. Serial sectioning failed to disclose evidence of new growth, hemorrhage or vascular thrombosis.

Anatomic Diagnosis

1. Adenocarcinoma of the pancreas, with metastases to liver, spleen, both kidneys and both lungs.

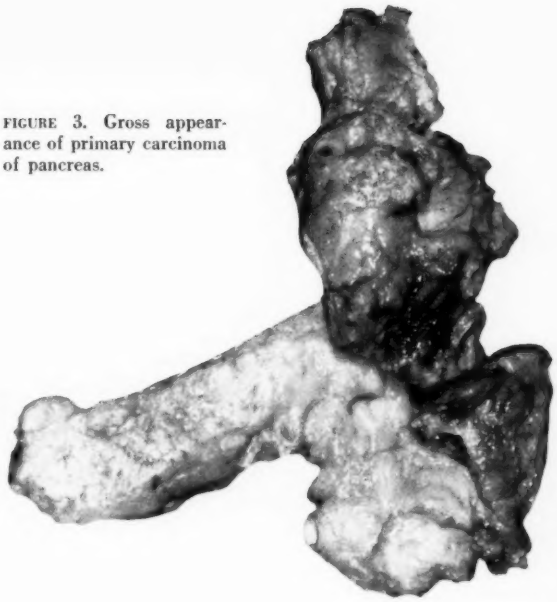

FIGURE 3. Gross appearance of primary carcinoma of pancreas.

2. Coronary thrombosis with occlusion and infarction.
3. Bronchopneumonia, bilateral.
4. Infarction of spleen, kidneys, left lung and peripheral vessels.
5. Infarction of peripheral vessels.

Discussion

PATHOLOGIST: There was a question as to whether the tumor was primary in the pancreas or lung. At autopsy, no connection could be found between any of the tumor masses of the lung and the bronchial tree, and on microscopic examination the tumor was quite classically the so-called sclerosing carcinoma of the pancreas.

DR. ABRAMSON: Were the thrombi on the heart valves of recent origin?

PATHOLOGIST: Yes. They were soft and readily brushed off, without injury to the endothelium, and microscopic examination showed the endothelium of the area to be intact.

We have seen multiple embolism of peripheral vessels in two other cases of carcinoma of the pancreas and liver.

DR. ABRAMSON: Your impression is that this was embolism rather than thrombosis?

PATHOLOGIST: Yes.

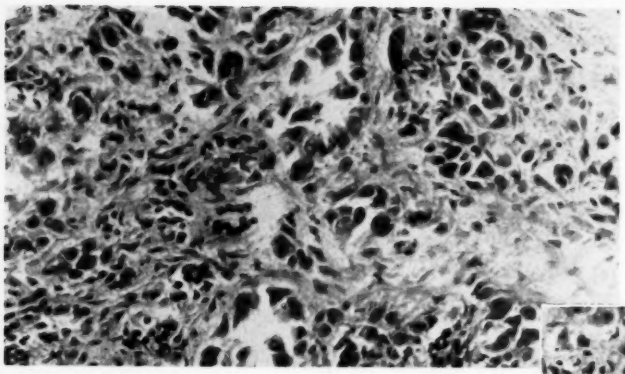

FIGURE 4. Adenocarcinoma of the pancreas.

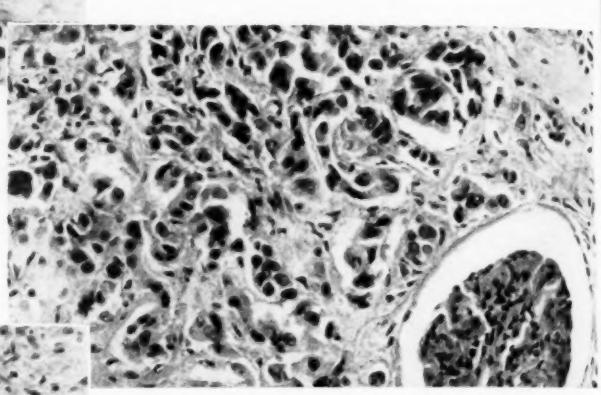

FIGURE 5. Adenocarcinoma of the pancreas, metastatic to the kidney.

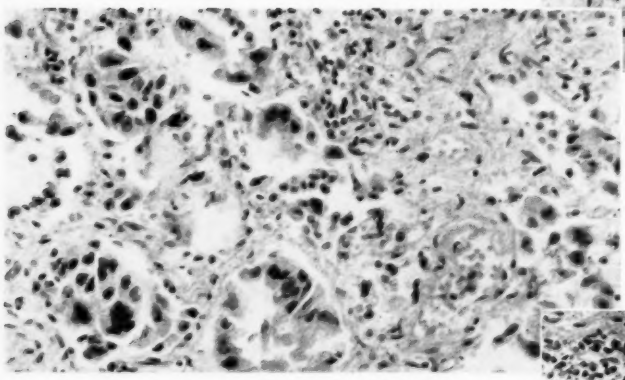

FIGURE 6. Adenocarcinoma of the pancreas, metastatic to the lung.

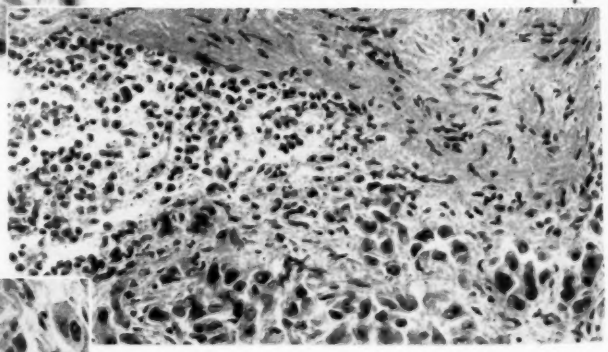

FIGURE 7. Adenocarcinoma of the pancreas, metastatic to the spleen.

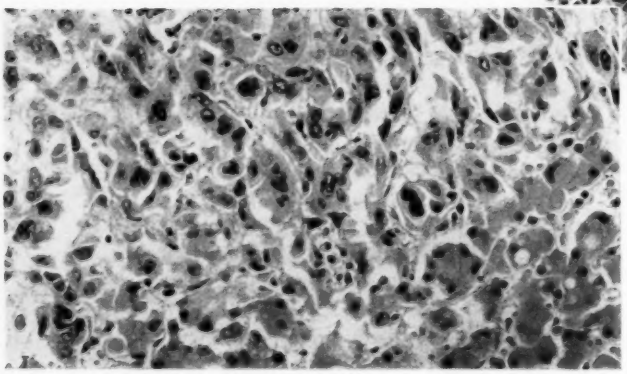

FIGURE 8. Adenocarcinoma of the pancreas, metastatic to the liver.

RESIDENT: Were the metastases in the liver the same as in the lung?

PATHOLOGIST: Yes.

DR. ABRAMSON: I also intended to discuss the question of the role that the injection of Pitressin played in the clinical course. There is a lot of doubt that Pitressin may cause constriction of coronary vessels and depression of cardiac efficiency, the latter being due to the diminution of oxygen supply consequent to the coronary constriction. The output of the heart is decreased despite elevation of blood pressure, and coronary flow is slowed.

In view of the onset of infarction after injection of Pitressin, one must assume causal relationship between the two. There would not be such a reaction in an individual with normal coronary vessels. However, it is conceivable that in an individual with coronary sclerosis or in one in whom signs of abnormal responsiveness of vessels to stimuli existed, as was noted in the present case, this drug might cause sufficient insult to coronary vessels to alter a coronary blood supply which is already impaired or markedly affected by external stimuli, to the point where it is inadequate to nourish the myocardium even at rest, and hence a myocardial infarction might result. It is therefore wise to exercise some caution in the routine use of Pitressin.

Postgraduate Clinical NOTES

46. CHEST PAIN

Pain in the chest is one of the commonest symptoms encountered by the physician. The differentiation of "coronary" pain or angina pectoris, due to coronary artery disease, from functional and other chest pain, has become an important and challenging problem. For example, in a recent survey of 1000 consecutive cardiac consultations, 61.2 per cent of the patients were found to have heart disease; three-fourths of these had coronary disease, 87 per cent of whom presented an anginal syndrome. Although almost 40 per cent of the 1000 patients were found to have *no heart disease, 64 per cent of this group complained of chest pain.* In these noncardiac cases, the pain was neurogenic in origin, or the result of such extracardiac conditions as spondylitis, fibrositis, peptic ulcer, gallbladder disease and hiatus hernia.

A. M. Master, H. L. Jaffe and L. Pordy, "Chest pain,"
The Medical Clinics of North America, May 1954

The Role of Medicine and Physicians in International Affairs

CHARLES W. MAYO*

Mayo Clinic and Mayo Foundation, Rochester, Minnesota

I WOULD be less than human if I did not express the deep feeling that I attach to the honor of being president of this association for 1955. I feel the honor deeply, not only because it has afforded me the opportunity to increase my medical knowledge and to mingle with my colleagues, but also because my uncle, Dr. Will, was president in 1933, and my father, Dr. Charlie, in 1935. There has been at least one occasion on which I have been introduced as the son of the Mayo brothers, which left me questioning whether Uncle Will was Mother.

CHARLES W. MAYO

The attainment of lasting peace is an objective more desired by more peoples of this earth than is any other. This is a self-evident truth. In spite of the supreme desire for a durable peace, there are those who, though wanting peace, firmly believe that war, whatever its apparent cause may be, is basically biologic in nature and only temporarily possible of deferment by man. Although there are arguments for this thinking, which from the start stifle the planning of efforts to attain world harmony and accord, the existence of such thinking seems a sad and negative commentary on civilization.

Our immediate concern is not the goal itself, but rather the mechanics, moral, legal and physical, by which our nation and others can advance toward the goal. True, individual man is entitled, yes, even obligated, to harbor idealistic objectives which have at heart human welfare; it is only thus that we become properly motivated. But actions designed to accomplish our aims must be practical and they must be taken step by step; this is a truism whether it concerns one person, a group of persons, a nation or even an organization of nations.

United Nations

A practical approach to the goal of peace

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Presidential address presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

is through the United Nations. This organization must be understood as an organization if one is to evaluate it properly as an instrument of peace. Written into its charter are many limitations that dictate what it can and cannot do. It is not a world federal government, it cannot tax anyone, it cannot draft a single soldier, it cannot step into any country to assist without a specific invitation from that country. On the other hand, it may be considered to be a world forum where knotty international problems are brought into the open for debate and resolution. There is no more powerful weapon for peace than the force of world public opinion founded on facts, not fiction.

An element of our population labors under the misconception that some things are "for free." Nothing could be more untrue. Somebody has to pay. When it comes to the question of cost, again we must be practical, particularly when we are spending the people's money. Hence we must ask, What is the product we desire? What is the cost? Is it worth it?

Our desire is peace. The cost? For the United Nations, the specialized agencies and the current special programs for the United Nations, the contributions of the United States for the fiscal year 1955 amount to a grand total of a little more than $92,500,000; that is 56 cents per person per year. Compare this with the nearly $400 per person per year represented by the military budget of the United States. Although we believe that military preparedness is a potent factor in the preservation of peace, particularly when that preparedness is maintained by a responsible and moral government such as ours, we are nevertheless impressed with the sharp contrast between 56 cents and $400.

For those who still are critical of the United Nations, its objectives and its cost, and who loudly proclaim, "United States, get out of the United Nations," and "United Nations, get out of the United States," there is the purely mercenary way of looking at the presence of this international organization in our country: the United Nations is a paying guest. Its presence in New York offers these financial advantages to the United States: (1) the investment of the entire pension fund, which amounts to $56,000,000, in the United States securities, (2) the spending of about $30,000,000 a year on such items as salaries and purchases in the United States, and (3) the spending of an unknown but estimated sum of $7,000,000 a year by delegates and aids.

Two more surprising facts about the United Nations are worth noting: First, 11 member nations contribute more per capita than the United States does and, second, the contribution of the Soviet Union is next to that of the United States.

Certainly, one must conclude that it is worth an annual contribution of 56 cents by each citizen to support such organized effort in the cause of peace.

From the international standpoint, there is, in addition, the personal contribution to peace, over and above the financial one, that each individual, regardless of race, color, creed or profession, can make through an enlightened interest in the means of achieving peace. That contribution entails first of all a more than passing acquaintance with those organizations, such as the United Nations, whose principal functions are the promotion of peaceful purposes. It entails a willingness on our part to be guided by reason and not by undirected emotion. It signifies that in our approach to the problems of others, as in the approach to our own problems, we must practice patience, understanding and tolerance.

Nationally, we have come to an old concept as though it were new. It is a wise concept even though it has been forced upon us by the demonstration once again that no one can buy friends with money. It is a simple concept—the concept of helping others to help themselves. The education of people to help themselves is not easy nor can it be done overnight; it means teaching teachers who in turn teach their own people. It is an investment, however, that pays both social and economic dividends; the needy nation, of course, benefits, so that, to look at it selfishly, the burden of continuing support is lifted from us. Thus, when it comes to rebuilding a nation after the devastation of years of ravaging war, or to assisting a backward country

toward the goal of self-government, the primary problem is to teach teachers in three principal fields, namely (1) public health, including medicine and sanitation, (2) agriculture and (3) engineering.

The first of these, public health, is where medicine plays an important role in international affairs. Health is a subject of common interest; when we protect the health of others, we, in a measure, protect ourselves. This is especially true of the spread of communicable diseases which has become an increasing hazard as the facilities for transportation have increased.

World Health Organization

The World Health Organization is associated with the United Nations but has its own officers and is administratively independent. The World Health Organization is not limited in membership to those in the United Nations but includes a total of 84 countries. It is because of this, too, that the chain of contact between our ambassador to the United Nations and the World Health Organization is through our Department of State, not through the secretary-general of the United Nations.

It was my privilege this year to serve as a delegate to the annual meeting of the World Health Organization held in Mexico City and to observe the functioning of this governmental member of the international health team. It exerts leadership and direction in the mass control of such diseases as malaria, which is of major concern to many countries, and yaws, which is important in southeast Asia and the Caribbean; it issues definitive technical reports of committees of international experts on such helpful subjects as nursing, mental health, sanitation, influenza, plague and a host of parasitic diseases; under its direction, 2000 professional persons in the various fields of health from countries that do not have the facilities for instruction are trained through fellowship grants.

The World Medical Association

As the American Medical Association is to the United States, so is the World Medical Association to the international scene—a representative organization on the professional level. It is made up of the leading medical societies of the world, of which our American Medical Association is one. In addition to organizational memberships, personal professional memberships are available. It is a sounding board for world medical opinion. The annual assemblies and council meetings consider the broad aspects of problems facing the physicians of the world.

Among the more important contributions of this young but potentially great association is the development of a sorely needed international code of medical ethics—a modern Hippocratic oath. It also sponsored the first World Congress on Medical Education. It recognizes, as all good physicians do, that progress in medicine and the advancement of our profession are dependent not only upon national endeavor of physicians but also upon international effort, and that we have the professional responsibility to see that the association is directed properly in the interest of all mankind.

There is close intertwining of the objectives of the World Health Organization and the World Medical Association. Each of these great organizations, representing governments and the medical profession in the international picture, has formally recognized the other. It is essential that they continue to cooperate in order to bring about effective effort such as a listing of international standards of drugs and dosage to be included in pharmacopoeias, and the development of international practices affecting doctors of medicine.

Conclusion

Because of the limitations of time, the great majority of us are not able to do justice to our own patients and at the same time take an active part in international affairs, but we should be informed on these matters and we should be aware of the fact that support of health programs beyond the confines of our country serves as an element of great strength in the foreign policy of our Department of State and in the protection of our own domestic health. We can be emissaries of good will for our country and our profession by inform-

ing ourselves, and then our communities, of the important part that promotion of health in underdeveloped countries plays in the preservation of peace and in the setting up of bulwarks against the spread of communism.

It is true that:

1. Sickness makes people poor.
2. Poverty makes people sick.
3. Healthy people can end poverty by "know-how."

The physician is familiar with this situation from his contact with individual patients; therefore, he can readily appreciate how such a situation applies to the larger social groups and can understand the international significance of this approach to foreign relations.

Medicine and physicians are destined to play an increasingly important role in the international scene with the objective of better world health for world peace.

Books Received

New books received are acknowledged each month. As space permits, books of principal interest to our readers will be reviewed more extensively. Reviews and additional listings will be found in this issue starting on page A-110.

Clinical Analgetics. By E. G. Gross, M.D., Professor and Head, Department of Pharmacology, State University of Iowa College of Medicine, Iowa City, and M. J. Schiffrin, Ph.D., Assistant Director of Clinical Research, Hoffmann-LaRoche, Inc., Nutley, New Jersey. 101 pages. 1955, Charles C Thomas, Springfield, Illinois. $3.00.

Child Behavior. By Frances L. Ilg, M.D., Director, and Louise Bates Ames, Ph.D., Director of Research, Gesell Institute of Child Development, New Haven, Connecticut. 364 pages. 1955, Harper and Brothers, New York. $3.95.

Aus- und Weiterbildung in der medizinischen Strahlenkunde. 41 pages. 1955, Georg Thieme Verlag, Stuttgart, Germany. Distributed in the United States and Canada by Intercontinental Medical Book Corporation, New York. $.85.

Of Research People. By George E. Burch, M.D., Henderson Professor of Medicine, Tulane University School of Medicine, New Orleans. 56 pages with 40 illustrations. 1955, Grune & Stratton, New York and London. $3.00.

Medical Research: A Midcentury Survey. Published for The American Foundation. Vol. 1, American Medical Research: in principle and practice, 765 pages; Vol. 2, Unsolved Clinical Problems: in biological perspective, 740 pages. 1955, Little, Brown and Company, Boston and Toronto. $15.00.

Chlorpromazine and Mental Health. Proceedings of the symposium held under the auspices of Smith, Kline & French Laboratories, June 6, 1955. 200 pages with 25 illustrations. 1955, Lea & Febiger, Philadelphia. $3.00.

Modern Nutrition in Health and Disease. Edited by Michael G. Wohl, M.D., Chief of Human Nutrition, Division of Biological Chemistry, Hahnemann Medical College and Hospital, Philadelphia, and Robert S. Goodhart, M.D., Scientific Director, The National Vitamin Foundation, Inc., New York, with 55 contributors. 1,062 pages illustrated. 1955, Lea & Febiger, Philadelphia. $18.50.

Functional Otology; The Practice of Audiology. By Morris F. Heller, M.D., Assistant Attending Otolaryngologist for Audiology, The Mount Sinai Hospital, New York, with Bernard M. Anderman, M.A. and Ellis E. Singer, M.A. 225 pages with 31 illustrations. 1955, Springer Publishing Company, Inc., New York. $5.50.

Practical Neurology. By Leo M. Davidoff, M.D., Professor and Chairman, Department of Surgery, and Emanual H. Feiring, M.D., Associate Professor of Surgery (Neurosurgery), Albert Einstein College of Medicine, New York. 442 pages. 1955, The Blakiston Division of the McGraw-Hill Book Company, Inc., New York. $7.00.

The Lacrimal System: Clinical Application. By Everett R. Veirs, M.D., Chief, Section of Ophthalmology, Scott and White Clinic, and Professor of Ophthalmology, The University of Texas Postgraduate School of Medicine, Temple Division. 159 pages with 73 illustrations. 1955, Grune & Stratton, Inc., New York and London. $7.50.

Thromboembolic Disease. By Geza de Takats, M.D., Division of Vascular Surgery, Department of Surgery, University of Illinois College of Medicine, Chicago. Edited by Michael E. De Bakey, M.D., Professor of Surgery and Chairman of the Department of Surgery, Baylor University College of Medicine, Houston, and R. Glen Spurling, M.D., Clinical Professor of Surgery, University of Louisville, Louisville. 55 pages. 1955, Charles C Thomas, Springfield, Illinois. $2.25.

Editorials

Postgraduate Medicine

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PROGRESS IN DIGESTIVE DISEASES — 1955

One of the greatest problems of medicine today is to adapt the tremendous advances made in such basic sciences as physiology, pharmacology, virology and biochemistry to the care of the patient. The important new drugs like MILTOWN®, reserpine and chlorpromazine, which are grouped under the general term of tranquilizers, undoubtedly will have a significant effect on the incidence and treatment of ulcer of the duodenum and stomach. The psychosomatic causation of these conditions is generally accepted. Conceivably the scientific use of these substances may diminish the need for psychiatric consultation.

During the past quarter century many different approaches to the problem of excess acid associated with ulcer have been made available. There are drugs like acetazoleamide which lower acidity when injected intravenously. The chemical approach which involves giving alkalis like the carbonates to counteract the acid has been supplemented by the mechanical approach (substances that coat the lining of the stomach), the neurologic approach (drugs that control the nerves involved in secretion), and the physiologic approach (cutting or otherwise inhibiting the action of the vagus nerve and removing various amounts of the stomach itself).

In the realm of the gastroenterologist is the liver, which is involved in numerous chemical and physiologic activities. The widespread occurrence of hepatitis is a cause for alarm. Today dogs are being inoculated against hepatitis; children suffer in epidemics which may not always produce jaundice but can cause lassitude, poor appetite, failure to gain weight, fever and bowel difficulties. Prevention and treatment with gamma globulin bring in the immunologist.

Medical scientists are attacking the solution of cirrhosis of the liver, often associated with chronic alcoholism, through a variety of measures. Recent research has shown that taking small amounts of alcohol in the usual manner does not harm the liver, as revealed by the results of a whole battery of liver function tests. Possibly, the harm that comes to the liver is the result of deprivation of essential vitamins, proteins or even of glucose during long sieges of alcoholism. New technics involve increased intake of glucose and decreased amounts of protein; yet only a few years ago all the emphasis was on the increased intake of an amino acid called methionine. ACTH and cortisone are being tried with a view to decreasing inflammation and to stopping the tendency to bleeding and anemia associated with this condition.

MORRIS FISHBEIN

BREAD

WITHIN our own lifetime, we have seen amazing developments in the manufacture of bread—man's most basic food next to milk. Indeed the nutritionists are still debating the many problems in this field. In a review[1] of the subject, Professor R. A. McCance of the University of Cambridge and his associate E. M. Widdowson point out that men began to cook cereals long before they made bread and that the history of bread began with the cultivation of wheat instead of barley. Just when white bread was developed by the removal of bran is not yet established. Apparently there are pictures made by ancient Egyptians which illustrate the sieving off of bran, and the Bible mentions "fine flour" as being superior to that in the general diet.

The ancient Greeks and Romans recognized at least four grades of flour. Indeed, the ability to have white bread instead of black or brown bread was an important class distinction. As far back as the time of Plato (400 B.C.) there were references to the fact that whole meal bread was more necessary for health and strength than refined flour, even though neither experimental evidence nor vital statistics were available to prove the point. Hippocrates considered that white bread was more nutritious and that whole meal bread made more feces. Indeed, Galen rated the four kinds of bread as varying inversely with the amount of bran in them because, in his opinion, "the greater the bulk of stools made by a given amount of bread the less nutritious that bread was likely to be."

In their very interesting article the British authorities trace the development of bread through medieval England, the eighteenth and nineteenth centuries and up to the time when Sylvester Graham, the vegetarian, began to emphasize whole meal bread, now called graham bread in the United States, and promoted its use almost as a religious cult. In fact, Graham said that separating the bran from the endosperm was tearing asunder what God had joined together in the grain. He also promoted the idea that bran bread provided strong frames and good health. Attention began to be transferred from the bran to the wheat germ and the nutritionists who began to make a science out of baking emphasized that "although whole meal flour contained more indigestible cellulose, it also contained more protein, fat and minerals than white flour." Still later, however, biologically minded scientists showed that the indigestible nature of the branny parts so increased the loss of nutrients in the stools that weight for weight the chemical advantages were more than counterbalanced by the physiologic drawbacks.

World Wars I and II turned intensive attention to the baking of bread, the principle of enrichment was introduced, we began to learn about the essential vitamins and minerals, and the question then was no longer "whether high extraction flour was better than white—nobody questioned that—but whether white flour enriched with B vitamins and iron was as good as the natural 80 or 85 per cent extraction flour."

Under the leadership of the British Medical Research Council, an extensive experiment was carried on in Wuppertal-Elberfeld in 1946. The experiments were held in a children's home in which there were 150 hungry youngsters. These children had been living on diets that had been short of calories, deficient in whole milk and otherwise unsatisfactory. Their total intake of animal protein was only some 8 gm. per day. These children were placed on diets consisting of 75 per cent of experimental breads and 25 per cent potatoes and vegetables. The breads were of unenriched 70 per cent extraction flour and a similar flour enriched with thiamine, riboflavin, nicotinic acid and iron. The experiments proved definitely that the children grew and improved equally well on either unenriched 70 per cent extraction flour or on 70 per cent enriched extraction flour. As a result of their studies the British authorities have concluded that it is not wise to generalize too widely from such experiments. They believe, for instance, that these experiments prove that white bread supplemented with a sufficiency of B vitamins gains nothing by the maneuver of fortification beyond that, and furthermore that such a diet which includes 25 per cent cereals and vege-

tables can be made so nutritious that it cannot be improved by a milk supplement. The concluding paragraph of their study is a beautiful piece of scientific philosophy:

> It is of course always possible that little attention will be paid to these experiments of ours until we are all dead and buried. It would be difficult now, for instance, for any administrator to go back on the policy of enrichment. The herd instinct "gives widely held beliefs a spurious validity irrespective of whether or not they are founded on any real evidence" (Beveridge 1950). Anything which threatens to make an adult change his beliefs, particularly if he has expressed them openly, is disturbing to him and it may safely be predicted —in fact it has already happened—that people who believe in the value of high extraction or have committed themselves to it will react to these results by attacking the evidence as best they can or by neglecting it, and so escape from its disturbing effects (George 1936). We shall not mind; we have had the fun of doing the work.

In an editorial[2] the *Lancet* traces the great battle that prevailed in England over this question of whole wheat versus white bread and agrees with the investigators that positive conclusions are not to be drawn from limited experiments. The situation has come to the appointment of a special panel which will determine for Great Britain, in the light of the scientific and medical evidence now available, the difference in the composition and nutritive value between national flour which is a 70 per cent extraction flour and flours of low extraction rate with or without the three token nutrients. The panel will advise as to whether any such differences are significant from the point of view of the health of the population.

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REFERENCES

1. McCance, R. A. and Widdowson, E. M.: Old thoughts and new work on breads white and brown. Lancet 2:205 (July 30) 1955.
2. Editorial: Bread. Lancet 2:235 (July 30) 1955.

SURVIVAL AND REHABILITATION AFTER CORONARY OCCLUSION

In one of the classic surveys of patients with heart disease and hypertension that have come from the clinics of Dr. Arthur M. Master, a report[1] published in 1954 on "Survival and rehabilitation after coronary occlusion" has great interest at this time. Dr. Master and his associates in the Cardiographic Laboratory of the Mount Sinai Hospital, New York, followed up 500 patients who had survived a coronary occlusion for from 1 to 29 years. Two out of every five patients had made a complete functional recovery. Three-fourths of all the patients were working and more than half of them had already lived more than five years after the attack. One out of every five patients survived the attack for more than 10 years. Death usually occurred as a result of another coronary occlusion or of congestive heart-failure.

Dr. Master emphasizes that the most reliable measure of recovery after coronary occlusion is the absence of symptoms related to the heart. When the physical examination, electrocardiogram, heart size and cardiac pulsation are normal, according to his observations, the patient has almost always made an excellent recovery. Important is the observation that the site of the infarction does not affect the prognosis after occlusion of a coronary vessel. The prognosis is better in younger patients, but on the whole the patient and the physician may be optimistic about the prognosis in coronary occlusion. Statistical studies have established that the majority of patients survive for many years and lead productive lives and those patients who return to work do at least as well as those who retire.

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REFERENCE

1. Master, A. M., Jaffe, H. L., Teich, E. M. and Brinberg, L.: Survival and rehabilitation after coronary occlusion. J.A.M.A. 156:1552 (December 25) 1954.